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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

ILLUMINA, INC.,
ILLUMINA CAMBRIDGE LTD.,

Plaintiffs,

v.

BGI GENOMICS CO., LTD., BGI AMERICAS CORP., MGI TECH CO., LTD., MGI AMERICAS, INC. and COMPLETE GENOMICS, INC.

Defendants.

Case No. 3:19-cv-03770-WHO
Case No. 3:20-cv-01465-WHO

DECLARATION OF DAVID SMITH IN SUPPORT OF OPPOSITION TO PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION

CONTAINS OUTSIDE ATTORNEYS' EYES ONLY INFORMATION

I, David I Smith, Ph.D., submit this declaration in support of Defendants' Opposition to Illumina's Motion for Preliminary Injunction. I declare as follows:

I. INTRODUCTION AND QUALIFICATIONS

1. My name is David I Smith.

2. My background, qualifications, and experience relevant to the issues raised in this proceeding are summarized below. A full description of my background and qualifications is set forth in my curriculum vitae, attached hereto.

3. I am a Professor, Consultant, Division of Experimental Pathology in the Department of Laboratory Medicine and Pathology at Mayo Clinic.

4. I am also Chairman of the Technology Assessment Group (TAG), Center for Individualized Medicine, Mayo Clinic. I have held this appointment since 2009.

5. I have more than 35 years of academic and practical experience in the field of molecular biology, including 30 years of experience with nucleic acid sequencing and amplification techniques.

6. I received my Bachelor's degree in Mathematics and Molecular Biology from the University of Wisconsin, Madison in 1974 and my Ph.D. in Biochemistry from the University of Wisconsin, Madison in 1978. My Ph.D. research involved the study of antibiotic resistance in bacteria and was a critical part of the cloning revolution. While I was a graduate student, I discovered two important restriction endonucleases (Pst1 and Kpn1) that were present in antibiotic resistant strains of *Providencia stuartii* (for Pst1) and *Klebsiella pneumonia* (for Kpn1).

7. After I obtained my Ph.D., I worked as a post-doctoral student at Albert Einstein College of Medicine, a Senior Research Scientist for Enzo Biochem, and a Post-doctoral Fellow at the University of California, Irvine. I began my first faculty position at Wayne State University in Detroit in 1986. While there, I advanced from an Assistant Professor to a full Professor. In 1996, I was recruited to the Mayo Clinic to be the head of their Cancer Genetics Program, which is part of the Mayo Clinic Comprehensive Cancer Program and to be a Professor and Consultant in the Division of Experimental Pathology, which is the experimental division within the Department of Laboratory Medicine and Pathology..

8. For more than 35 years, I have conducted research in molecular biology, with a special emphasis on studying the roles that the common fragile sites, which are unstable regions in the genome that are hot spots for mutations, play in cancer development. My laboratory has also studied the various ways that human papillomavirus is involved in the development of different cancers. Throughout my career, I have also used state-of-the-art molecular biology tools to study molecular alterations underlying cancer development and to translate these findings into cancer therapies.

9. For decades, I have taught students regarding genome analyses and genetics. Currently, I teach a class on molecular technologies to incoming graduate and medical students at the Mayo Clinic, with a specific focus on the newest DNA sequencing technologies. I taught this class from 2001 through 2006, when the next generation sequencing revolution began following the introduction of the 454 next generation sequencing platform. Thus, I experienced first-hand how this one technology significantly transformed the world of DNA sequencing. In addition, I teach fellows in the Department of Laboratory Medicine and Pathology about the DNA sequencing revolution and how this is going to be a real game-changer for how we clinically manage our patients. I also provide expertise to many other people in other Departments at the Mayo Clinic who are interested in utilizing the power of advanced sequencing technologies for their specific research or clinical needs.

10. I have published more than 250 scientific articles related to gene synthesis, cloning, gene mapping, and DNA and genome sequencing. Moreover, I was involved in the mapping and sequencing of human chromosome 3 during the development of the first draft sequence of the human genome. I began working with microarray technologies shortly after joining the Mayo Clinic in 1996. I also obtained the first grants to obtain the next generation sequencing platforms including 454 and Illumina, and, beginning in 2007, was responsible for developing the necessary infrastructure required for next generation sequencing at the Mayo Clinic.

11. From 1999-2009, I was the Chairman of the Research Resource Facilities Sub-Committee, which included the responsibility of supervising the running and financial activities of a number of research Core Facilities, including the DNA sequencing Core.

12. I serve on the editorial boards for *Cytogenetics and Genome Research* and the *Journal of Next Generation Sequencing*. In addition, I routinely review manuscripts in my various areas of

expertise for a number of other prestigious Journals.

13. Moreover, I have received several honors throughout my career related to my research in molecular biology. In my opinion, the most significant of these are: my selection as the recipient of the Basil O'Conner Starter Scholar Research Award from the March of Dimes in 1988 for my early work shortly after setting up my first laboratory at Wayne State University as well as my receipt of "The Innovator" award from the Department of Laboratory Medicine and Pathology at the Mayo Clinic in 2009 for my early work on next generation sequencing.

14. Since 1986, I have worked in molecular biology laboratories using and evaluating techniques and technology for gene sequencing and amplification.

15. Since 1986, I have worked in molecular biology laboratories using and evaluating techniques and technology for gene sequencing and amplification. I brought microarray technology to the Mayo Clinic in 1997, routinely utilized Sanger Sequencing methods (starting in the days of hand loading radioactive reactions into sequencing gels through the development of capillary electrophoresis (CE) and then automated CE machines). I was one of the first investigators at the Mayo Clinic to utilize microarrays and have subsequently utilized them to study gene expression in different cancers, and my laboratories have regularly utilized Sanger sequencing methods.

16. When next generation sequencing became commercially available with the introduction of the 454 platform, I was responsible for procuring the necessary funds to enable the Mayo Clinic to purchase its first 454 sequencing machine, and I utilized that machine in my laboratory studies. In addition, I was also responsible for helping develop the necessary infrastructure for next generation sequencing required by the Mayo Clinic. I also worked with many other investigators and clinicians at the Mayo Clinic to help them utilize the powerful next generation sequencing technology for their research. Therefore, I have extensive experience in genomics, single molecule analysis, polymerase chain reaction ("PCR"), emulsion PCR, DNA sequencing, and detection techniques.

17. Accordingly, my expertise in the field of molecular technologies includes next generation sequencing and the sample preparation required for those methods. As shown above, my responsibilities have included implementing and supervising those technologies at the institutions for

which I worked. For the past two years I have written the Next Generation Sequencing Buyers Guide for Front Line Genomics which compares and contrasts the various next generation sequencing platforms and provides advise to the readers about the best technologies to utilize for specific types of work.

18. A copy of my CV is attached hereto as **Appendix A**, which includes my testifying experience in the past four years.

19. I have no financial interest in, or affiliation with, the Plaintiffs or Defendants. I am being compensated for my time at the hourly rate of $400/hour. My compensation is not in any way dependent on the content of my testimony or the outcome of the proceedings.

II. ISSUES CONSIDERED

20. I understand that Plaintiffs Illumina, Inc. and Illumina Cambridge LTD. (collectively, "Illumina") allege that certain of Defendants' products infringe certain claims of U.S. Patent Nos. 7,771,973, 7,566,537, 7,541,444, 9,410,200, and 10,480,025, which are owned by Illumina Cambridge and licensed to Illumina, Inc.

21. I understand that Defendants' accused products include:

a. MGISEQ-T7, MGISEQ-2000, MGISEQ-200, BGISEQ-500, BGISEQ-50, DNBSEQ-T7, DNBSEQ-G400, DNBSEQ-G50, and DNBSEQ-G400 FAST sequencers;

b. MGISP-960, MGISP-100 sample preparation systems;

c. MGIFLP-SL200 and MGIFLP-L200 workflow systems; and

d. "standardMPS" and "CoolMPS™" sequencing reagents and kits.

22. I understand from Defendants' Counsel that Illumina has sought a preliminary injunction and the following factors will be considered by the court in determining to grant the injunction: (1) whether Illumina is likely to succeed on the merits, (2) whether it is likely to suffer irreparable harm in the absence of preliminary relief, (3) whether the balance of equities tips in its favor, and (4) and whether an injunction would disserve in the public interest.

23. For purposes of my analysis, I have been asked by Counsel for Defendants to address the fourth factor, whether an injunction would disserve the public interest. Thus, my focus in this declaration is the potential harm to the public that is will be caused if a single company (*i.e.*,

Illumina) is permitted to continue to have a monopoly on advanced DNA sequencing technologies, and how this fails to serve the greater good for all. I will also more briefly address certain issues related to the second factor, whether Illumina is likely to suffer irreparable harm in the absence of preliminary injunctive relief.

III. INFORMATION CONSIDERED

24. This declaration is provided based on my personal and professional experience in the field of DNA sequencing. I have experience both as a researcher doing both basic science and translational research and have provided expertise to many other researchers and clinicians at the Mayo Clinic. I have also helped to Mayo Clinic to set up the needed infrastructure for advanced DNA sequencing technologies, including those from Illumina. This includes help in selecting the proper next generation DNA sequencing machines for different applications. I was involved in the purchases of the original 454 sequencing machine at the Mayo Clinic, their first Illumina Genome Analyzer (in 2007), the original Pacific Biosciences sequencing machine, and I also wrote a proposal and obtained approval from Oxford Nanopore so that the Mayo Clinic could work with the very earliest version of the MinION sequencer.

25. I have reviewed and considered the documents identified in **Appendix B** during the preparation of this declaration. I have selected a subset of those documents to support the opinions set forth herein, and those have been cited to explicitly.[1]

IV. FACTUAL BACKGROUND

A. History of Massively Parallel Sequencing ("MPS")

26. In order to generate the first draft sequences of the human genome in 2000, it was necessary to develop high throughput automated machinery that could take optimal advantage of di-deoxy nucleotide chain termination sequencing (otherwise known as Sanger Sequencing). That culminated in the 96 capillary Applied Biosystems 3700 Sanger Sequencing machine (CE- for capillary electrophoresis),[2] which was capable of producing 75 Kbs of DNA sequence every 4 hours.

[1] The cited exhibits are attached to the Declaration of Katie J.L. Scott (exhibits beginning with a "D" number) or were previously filed (D.N.).

[2] D.N. 12-40 (Van Oene Decl., Ex. NN) at 525-26

This machine decreased the cost of sequencing substantially from anything previously available. By running hundreds of these machines in parallel over several months, it was possible in 2000 to generate sufficient DNA sequences from an individual to produce those first draft sequences. However, the total cost to generate sufficient human sequences to assemble a draft sequence of that genome in 2000 was still 200 million dollars. The two most important reasons are (1) that each individual DNA fragment had to be cloned into a small *E. coli* plasmid and replicated in bacteria, and (2) that each sequencing reaction of each cloned fragment still required at least 10 microliters of reagents and that millions of these reactions were required to generate sufficient DNA sequence to assemble that sequence into some draft form.

27. Automated DNA sequencers made it possible to generate the first draft sequences of the human genome, but CE-based technologies are still way too expensive an approach to generate sequences of large numbers of individuals.[3] The solution to generate orders of magnitude more sequence data for an even smaller amount of input dollars was the development of technologies which all share that their approach is to perform massively parallel DNA sequencing ("MPS"). There are actually two generations of MPS technologies. All first generation MPS technologies are dependent upon techniques to amplify individual DNA molecules, which are then sequence interrogated. The amplification increases the overall signal strength, as individual bases are characterized, which results in increased sequence accuracy, but at the cost of a reduced read length of the sequences determined. Second generation MPS technologies do not need to amplify DNA fragments and are capable of generating extremely long sequence reads. However, this comes at the cost of overall sequence accuracy and lower overall sequence output than some of the first generation MPS technologies.

B. First Generation MPS Techniques

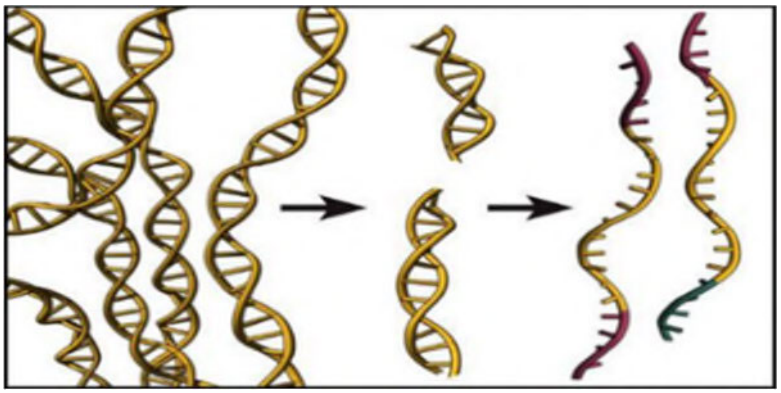
28. All first generation MPS technologies require some technique to amplify individual DNA molecules to between a few hundred to several hundred thousand copies. There have been three major different ways that this has been done. The first one developed is called emulsion PCR and is based upon amplifying individual DNA fragments on tiny microbeads in water droplets in a lipid

[3] D.N. 12-40 (Van Oene Decl., Ex. NN) at 525-26.

emulsion. The second is called bridge amplification, which is capable of amplifying individual DNA fragments without the messy need for oil and water emulsions. Both of these techniques amplify DNA fragments through PCR amplification. In contrast, the third technique is not reliant upon PCR amplification. Instead, it instead amplifies small fragments by ligation to an adenoviral vector and then this is linearly replicated to several hundred copies. The amplified DNA fragments collapse into tiny DNA nanoballs, thus this technology is now called DNB-based amplification.

i. Emulsion PCR

29. The emulsion PCR technique begins with the DNA to be sequenced being fragmented and then having oligonucleotide primers annealed to both ends, as shown below.



30. The primers that are annealed to the DNA fragments are complementary to primers on the surface of DNA capture beads to permit the fragments to be hybridized to the beads. The library of DNA fragments is then emulsified with oil and water, in the presence of very large numbers of the DNA capture beads, and the necessary reagents for PCR amplification of individual DNA fragments.[4] A tiny water droplet that contains a bead and a single DNA fragment can then amplify that fragment to large numbers by PCR within the bead.

31. Each cycle, more copies of the fragment are covalently ligated to the oligonucleotides on the bead. After amplification, the water droplets need to be lysed and the beads with amplified DNA on them purified from non-amplified beads by density gradient centrifugation.[5] These beads are then ready for DNA sequence interrogation.[6]

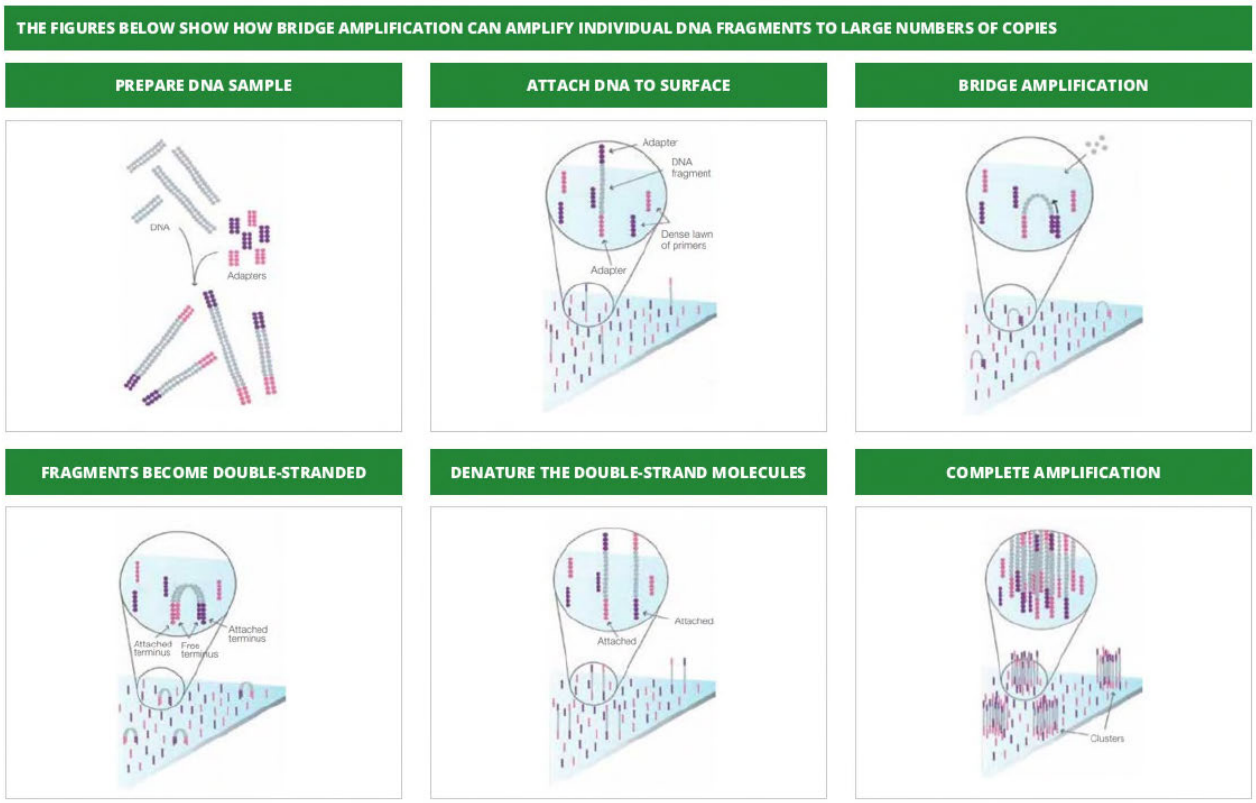
[4] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-71.

[5] *Id.*

[6] *Id.*

ii. Bridge Amplification

32. In the bridge amplification technique (illustrated below),[7] the DNA is fragmented and two different primers are annealed to the ends of all the fragments.[8] The surface of the flow cell has oligonucleotides that are complementary to the oligonucleotides at the ends of all the fragments coating the surface.[9] In this technique, an oligonucleotide at one end of the fragment binds to its complement on the flow cell and then that fragment's other end "bridges" to bind to its complement, hence the name.[10] This technique readily produces amplified clusters containing 30,000 copies of each original DNA fragment, and without the need for the oil and water emulsions.



iii. DNB-Based Linear Amplification

33. In this linear amplification technique (illustrated below),[11] DNA Nanoballs (DNBs)

[7] D.N. 12-36 (Van Oene Decl., Ex. JJ) at 9.

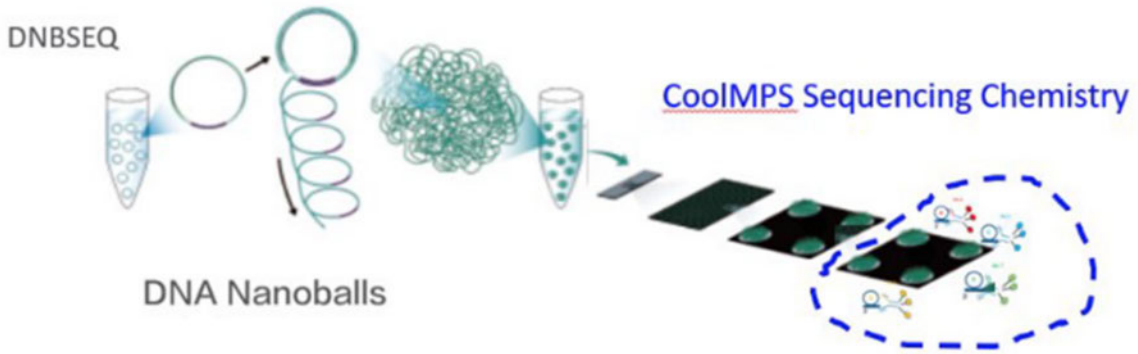
[8] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-ILMNBGI0160071.

[9] *Id.*

[10] *Id.*

[11] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-ILMNBGI0160071; D.N. 12-20 (Van Oene Decl., Ex. T) at 12.

are produced by ligating 200-500 base fragments with an adapter into a circle.[12] In the presence of the appropriate polymerase, the circularized DNA fragments are linearly copied 100-1000 times (without any PCR amplification).[13] The single stranded fragments fold onto themselves into a DNA nanoball which can then be deposited into a patterned flow cell for subsequent sequence interrogation.[14] Since this method of amplification makes all the DNA copies from one original copy, it does not produce the clonal PCR amplification errors that are associated with the other two techniques used to amplify DNA fragments.



C. First Generation MPS Platforms

i. 454: The First Viable MPS Machine

34. In 2006, the company 454, run by Jonathan Rothberg and colleagues, came out with the 454 Genome Sequencer 20 which was capable of generating 20 megabases of sequence data in a 12 hour run.[15] This was the true birth of the MPS revolution. The 454 system starts by amplifying individual DNA fragments onto 28 micron beads to generate up to one million copies of each amplified fragment using emulsion PCR. To analyze the sequence on those amplified beads, 454 utilized fiber optic cables to produce picrotiter plates that contained 1.5 million tiny 30 micron wide

[12] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-ILMNBGI0160071; D.N. 12-20 (Van Oene Decl., Ex. T) at 9-13.

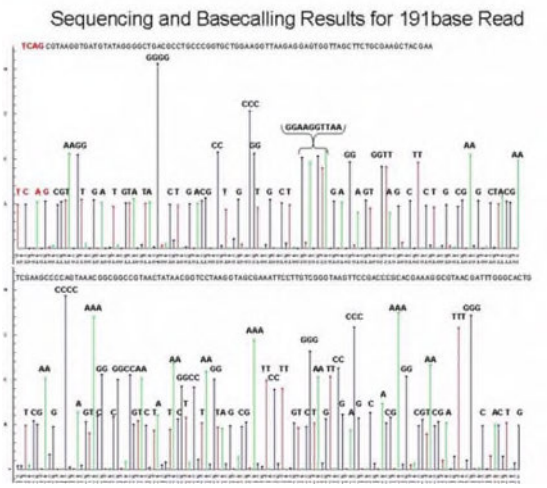
[13] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-ILMNBGI0160071; D.N. 12-20 (Van Oene Decl., Ex. T) at 9-13.

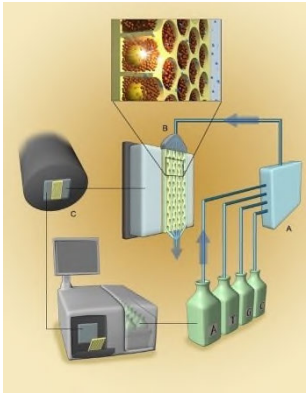
[14] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-ILMNBGI0160071; D.N. 12-20 (Van Oene Decl., Ex. T) at 9-13.

[15] *See* D.N. 12-40 (Van Oene Decl., Ex. NN) at 526-27; Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160076.

wells.[16] Beads with amplified DNA on them are deposited into the wells of the picrotitre plates with the needed reagents for base incorporations and two enzymes that cumulatively produce a flash of light when a base is successfully ligated to the ends of the amplified fragments (called pyrosequencing).[17]

35. On the 454 sequencing platform, the sequence of the amplified DNA fragments on the beads is determined by sequentially flowing individual nucleotides (A followed by C, then G and T) over the surface of the picotitre plate to see if one of those nucleotides is incorporated as the next available nucleotide. The 454 sequencing technology adds one unblocked nucleotide at a time and then determines the which wells incorporated that nucleotide by taking a photograph with a CCD camera looking for flashes of light.[18] This is then followed by the three other nucleotides, with a picture taken after each addition.[19] All of this is illustrated in the two figures below including a depiction of the type of sequence data that was generated off of a single first generation amplified bead.





36. The most incredible thing about the 454 sequencing platform was that at its inception it was capable of generating over 250 times more data per run than its predecessor, the Applied

[16] *See* D.N. 12-40 (Van Oene Decl., Ex. NN) at 526-27; Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160076.

[17] *See* D.N. 12-40 (Van Oene Decl., Ex. NN) at 526-27; Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160076.

[18] *See* D.N. 12-40 (Van Oene Decl., Ex. NN) at 526.

[19] *See* D.N. 12-40 (Van Oene Decl., Ex. NN) at 526.

Biosystems 3700. In addition, this sequencing platform improved for several years resulting in increased sequence output at a reduced cost. By 2008, the updated 454 sequence machines were capable of generating 500 MBs of sequence output per run. In 2008, the company 454 generated a draft sequence of the genome of James Watson and the cost of doing this on their machines was then only 1 million dollars (a 200-fold decrease as compared to CE-based sequencing).

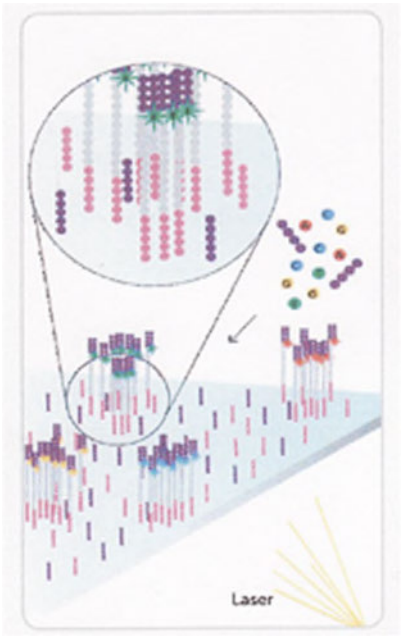
37. There are a couple of limitations to the 454 sequencing platform in addition to the very cumbersome techniques required to performing emulsion PCR amplifications. The nucleotides that flood the sequencing plate to determine which wells incorporated that base are wild type unblocked bases. If there is just a single nucleotide that can be added in a specific well, that well will add it when that nucleotide floods the well. However, if there is a string of the same nucleotide (a homopolymer), all those nucleotides will be incorporated (this is seen on the figure above where multiple nucleotides have been added and the signal strength increases). While it is easy to discern one from two, or three nucleotides, it is very different to tell the difference between 9 and 10, or more nucleotides in a homopolymer. Thus, especially in the clinical setting, the inability to correctly call long homopolymers is a potential problem. Another limitation to this platform was that although it was capable of increasing throughput 25-fold over its lifetime, it was not capable of ever generating more than 500 Mbs of sequence data per run.

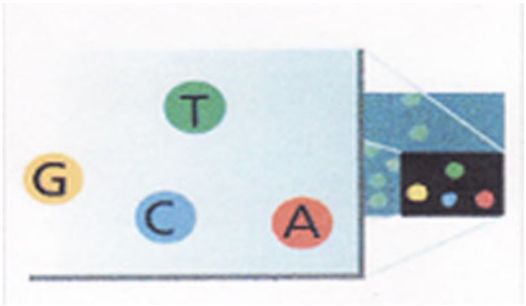
ii. The Illumina Sequencing Platform

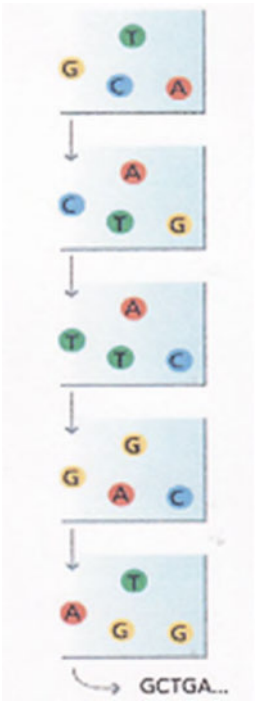
38. The second commercially viable MPS technology came from the company Solexa, which was purchased by Illumina in 2006. In 2007, they released their Genome Analyzer which was capable of generating 1 Gigabase ("Gb") of sequence output per week long run. The Illumina platform uses the PCR-based methodology of bridge amplification to amplify individual fragments up to 30,000 copies and these are bound to fixed positions on an 8-lane flow cell.[20] To determine the sequence of the amplified fragments, Illumina utilized four different colored fluorescent tags (one for each of A, C, G, and T), which are attached directly to the nucleotides via a reversible linkage in

[20] *See* Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-ILMNBGI0160072; D.N. 12-40 (Van Oene Decl., Ex. NN) at 527-29.

such a way that only a single nucleotide can be attached at a time.[21] The flow cell containing the amplified DNA clusters is flooded with all four fluorescently labeled nucleotides.[22] After base incorporations, the flow cell is scanned to determine which nucleotide has ligated to which amplified cluster.[23] After taking the picture of nucleotide incorporations, the fluorescent tags are chemically removed which also leaves the ends of the amplified cluster capable of incorporating the next nucleotide.[24] The flow cell is again flooded with all four labeled nucleotides to see which nucleotides are added at the second position.[25] This process is then repeated to determine a sequence for the millions of amplified DNA fragments, as shown below.







[21] *See* Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070-ILMNBGI0160072, ILMNBGI0160075; D.N. 12-40 (Van Oene Decl., Ex. NN) at 527-29.

[22] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160070, ILMNBGI0160075; D.N. 12-40 (Van Oene Decl., Ex. NN) at 527-29.

[23] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160075; D.N. 12-40 (Van Oene Decl., Ex. NN) at 527-29.

[24] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160075; D.N. 12-40 (Van Oene Decl., Ex. NN) at 527-29.

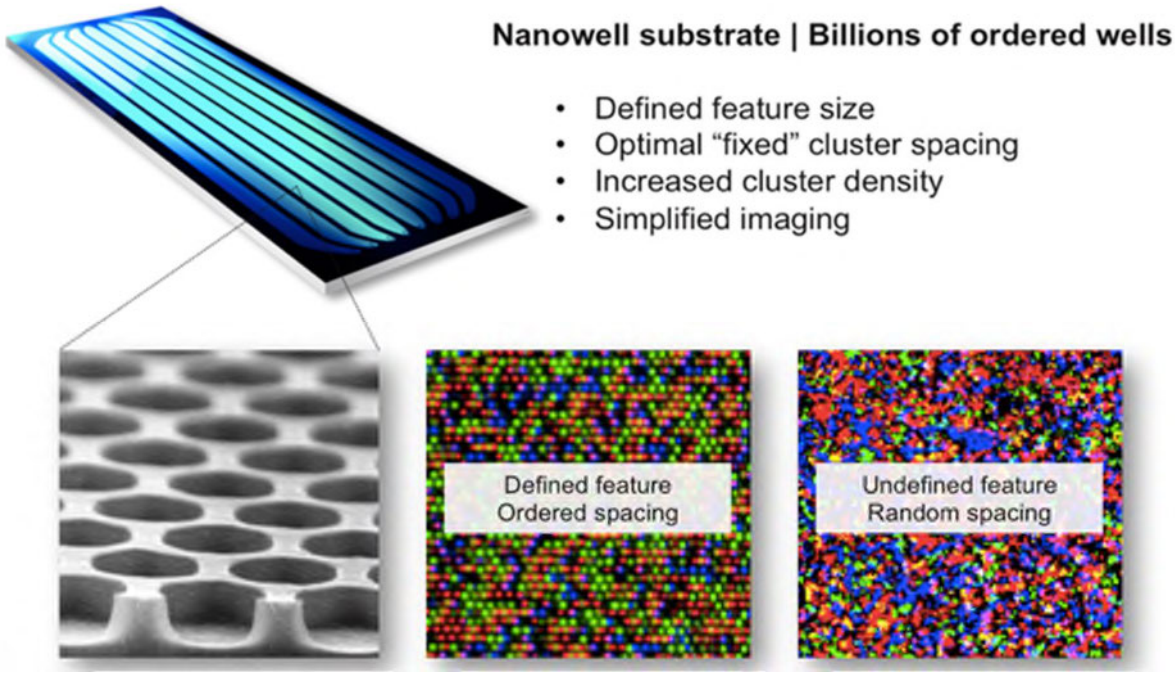
[25] I Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160075; D.N. 12-40 (Van Oene Decl., Ex. NN) at 527-29.

39. Illumina's sequencing technique uses sequential addition of labeled complementary nucleotides to the amplified clusters, which results in each cluster being tagged with a different color depending upon the identity of nucleotide base that was incorporated.[26] This process is repeated with such that the sequence of the amplified fragments at each cluster can be determined as is shown in the third picture above.[27]

40. The original Genome Analyzer was only capable of generating 30 base pair reads, but could still generate 1 Gb of short DNA sequences.[28] Over the next several years, the read length was increased on this platform (to 150 bp) and the total number of amplified fragments that could be analyzed was also dramatically increased. At the end of the lifetime of this instrument (2010), the Genome Analyzer was capable of generating 80 Gbs of sequence output per run (an 80-fold improvement in 3 years).[29]

41. The Illumina machine that replaced the Genome Analyzer in 2010 was the HiSeq 2000. The HiSeq 2000 increased the total number of amplified fragments that could be sequenced and was capable of generating 200 Gbs of sequence output per run. However, pretty soon afterwards the density of clusters on the flow cells was starting to get so high that it was difficult to discern some of the clusters from each other. Illumina used the technique that was introduced by Complete Genomics, which was to only amplify DNA fragments within tiny, predetermined regions on the flow cells, rather than to generate random clusters on the surface of the flow cell. As shown below, Illumina's change from random regions of amplified clusters to a pattern results in very nice resolution signal from each amplified cluster (just compare the easily discernible individual amplified fragments in the middle picture to the one on the right).[30]

[26] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160075.
[27] *Id.*
[28] *Id.*
[29] *Id.*
[30] *Id.*



42. By adopting patterned flow cells (as shown above), Illumina has the first sequencing platform that was able to generate DNA sequence yields in excess of 1 terrabase ("Tb") (this is a 1,000-fold increase from the output on the original Illumina Genome Analyzer). The current generation of highest output Illumina sequencers, the Novaseq, is capable of generating 6 Tb of sequence data on two flow cells. Using the highest output flowcell on the NovaSeq system it is now possible to generate sufficient whole genome sequence data for a single individual for the phenomenally low reagent price of $500-600.[31] However, as discussed later, this is just the cost of the sequencing part of whole genome sequencing.[32] Illumina now produces an entire family of sequencing machines in addition to the Novaseq machines that vary in both their price, sequence output, and application.

43. The original Illumina Genome Analyzer was capable of generating 1 Gb of sequence data per run. Today, the NovaSeq machines can produce up to 6 Tbs of sequence data per run. However, even the lowest output Illumina machine (the iSeq 100) is now capable of generating 1.2 Gb of sequence output in a 19 hour run. A desktop machine that Illumina now produces that is

[31] Ex. D49 (4/9/2020 Van Oene Tr.) at 56-59. I have also personally heard of reagent prices as low as $475 per genome.

[32] *Id.*

routinely used in clinical laboratories (the NextSeq 550 series) can generate 120 Gbs of sequence output in just one day. What this demonstrates is that the output on the largest Illumina sequencing machines also actually drives increased sequencing output on the smaller Illumina machines, much like development of materials for use in space has resulted in useful building materials or advances for high-end race cars have led to developments in the automotive industry.

iii. The Ion Torrent Sequencing Platform

44. The Ion Torrent sequencing platform was also developed by Jonathan Rothberg and shares many of the exact same strategies to both amplify the DNA fragments and to test naked nucleotides for incorporation, as his first platform, the 454 sequencer.[33] DNA fragments are first amplified onto 5 micron beads using emulsion PCR to up to 50,000 copies. There are less copies amplified on these beads than on the 28 micron beads utilized in the 454 sequencing platform due to the decrease in surface area on the smaller beads. The Ion Torrent system gets its name because when a base is incorporated there is a hydrogen ion released, so if a bead with amplified DNA on it incorporates the naked base presented to it there would be a torrent of ions flowing off that bead.[34] That torrent of hydrogen ions decreases the pH in that well and that is the technique Ion Torrent utilizes to determine the sequence of the amplified fragments on the beads.[35] The flow cells are run using the exact same strategy as the 454 sequencing platform, except now the method of base incorporation detection is the ion torrent changing the pH in that well when one specific nucleotide is incorporated into the fragment that is being sequenced.[36]

45. The Ion Torrent has all the weaknesses of the 454 system when it comes to sequencing homopolymers, and still utilizes the very cumbersome emulsion PCR amplification procedure to amplify individual DNA fragments onto the 5 micron beads. The figures below show some of the features of the Ion Torrent sequencing system.

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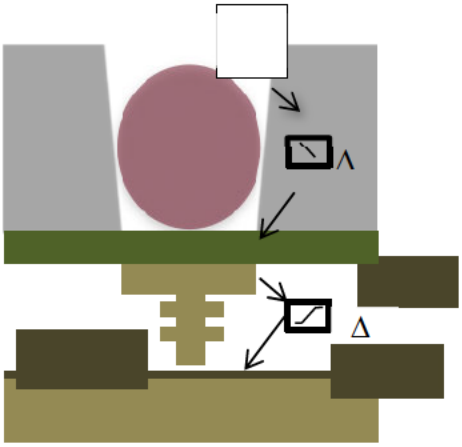
[33] *See* Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160074, ILMNBGI0160076.

[34] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160074, LMNBGI0160076.

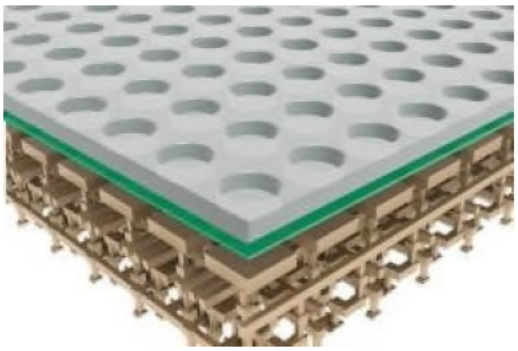
[35] *See* Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072, ILMNBGI0160074, LMNBGI0160076.

[36] *Id.*

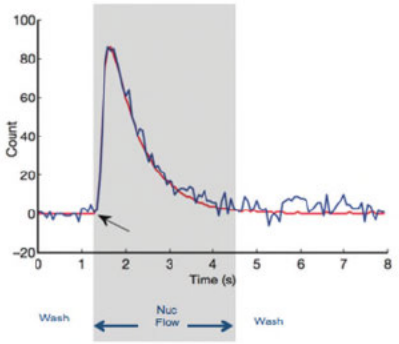
The ion torrent sequencing chip



A bead with amplified DNA fragments in a sequencing well



Ion Torrent sequencing chip with wells for individual beads with amplified DNA



Nucleotide incorporation detected by a change in pH in that individual well

46. The Ion Torrent system has increased output from the original Personal Genome Sequencing Machine (PGM), but the sequence output on this machine is still only a small fraction of what can be obtained on the high throughput Illumina machines. The Ion Torrent system has proven to be very useful for the sequencing of small and medium-sized gene panels and one of its strengths is a that it requires less input DNA to produce decent libraries for sequencing. However, the majority of sequencing that is now done throughout the world is on Illumina sequencing machines. Illumina itself estimates that over 90% of sequencing data in the world has been generated on Illumina systems.[37]

[37] P.I. Mot. 19-21.

iv. DNB Nanoball (DNB) Sequencing

47. The third strategy utilized to amplify DNA fragments was developed by Dr. Rade Drmanac and co-workers at Complete Genomics, and is called DNB-based sequencing. Each cloned fragment is linearly amplified to a copy number of around 300 and the single stranded amplified fragments collapse into tiny DNA nanoballs which can then be deposited into patterned flow cells for subsequent sequence analysis.[38]

48. Following acquisition by BGI, CGI began to develop its own sequencing-by-synthesis (SBS) chemistry for use by its affiliate, BGI Genomics, which provides sequencing as a service in China and other parts of the world. More recently, Dr. Drmanac and his team have developed an new approach to SBS that is not at all dependent upon incorporating fluorescently labeled bases, where the nucleotide base is linked to a cleavable label. In their new strategy, "cold" (unlabeled) bases are utilized which have a block preventing more than a single base addition.[39] To determine which base has been added, a 4 different base-specific labeled antibodies are used to bind to the nucleotide base and the removable blocking group.[40] After taking a picture of the chip, the antibodies are washed away and the blocks are chemically removed from the last base incorporated so that the next base incorporation can occur and be detected.[41] This is illustrated on the figure (below).[42] This sequencing chemistry is referred to as "CoolMPS," and is depicted in the Figure below.[43]

[38] D.N. 12-20 (Van Oene Decl., Ex. T) at 10-13; D.N. 12-19 (Van Oene Decl., Ex. S) at 19-24.

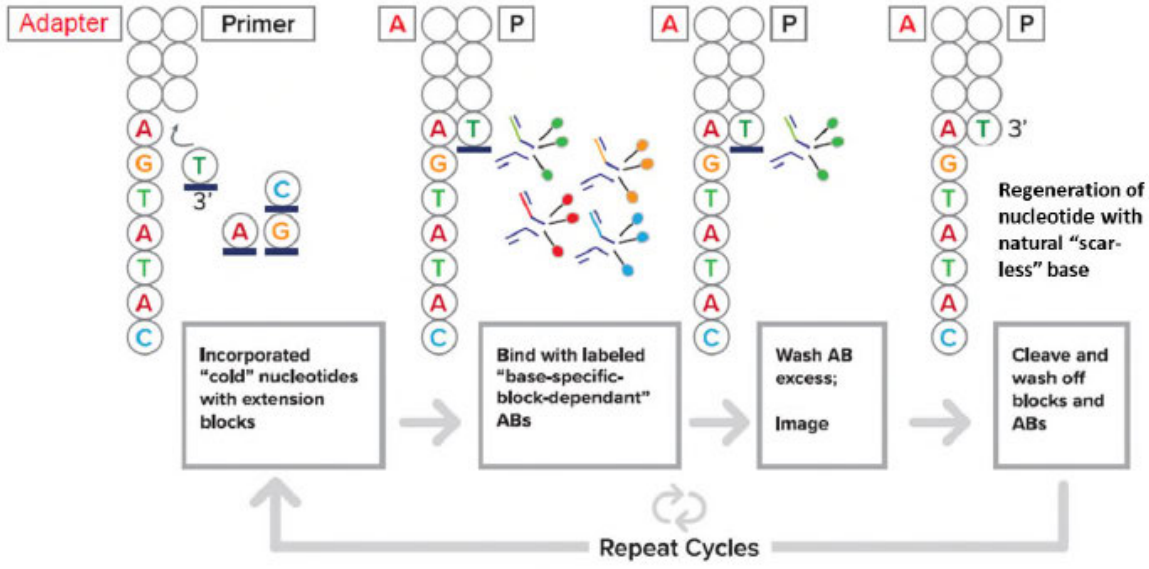
[39] D.N. 12-20 (Van Oene Decl., Ex. T) at 15; D.N. 12-19 (Van Oene Decl., Ex. S) at 31-34; D.N. 12-39 (Van Oene Decl., Ex. MM) at 2-7.

[40] D.N. 12-19 (Van Oene Decl., Ex. S) at 31-34; D.N. 12-39 (Van Oene Decl., Ex. MM) at 2-7.

[41] D.N. 12-19 (Van Oene Decl., Ex. S) at 31-34 D.N. 12-39 (Van Oene Decl., Ex. MM) at 2-7.

[42] D.N. 12-39 (Van Oene Decl., Ex. MM) at 2.

[43] D.N. 12-39 (Van Oene Decl., Ex. MM).



49. There are a number of advantages to the "CoolMPS" approach to sequencing DNA. The first is that by utilizing cold (unlabeled) nucleotides with a 3' blocker and fluorescently labeled base-specific antibodies, CGI solved the problem of a residual "scar" being left which frequently occurs with both the Illumina SBS strategy and the first BGI sequencing strategy. Ultimately this means that there is much greater capability of increasing read length of the amplified fragments, as the scars cause problems with future base incorporations. In addition, each antibody has multiple fluorescent groups attached to it, which increases signal strength. Thus, there is room for substantial further improvements, such as the utilization of smaller DNA nanoballs and still having sufficient detectable signal for accurate sequencing. This then offers two cost-saving advantages. The first is the requirement for less sequencing reagents and the second is the capability of placing more nanoballs on the same surface area, both resulting in increases in DNA sequence output at a decreased cost.

50. The currently available highest throughput BGI machine, the DNBSEQ-T7 (shown below), is capable of generating 6 Tbs of sequence output per one-day run and the sequence obtained on this machine is very comparable to that obtained on an Illumina NovaSeq. I have had whole genome sequencing performed on a number of cancer cell samples on both machines. Since the read length and the output on the DNBSEQ-T7 is quite similar to what is observed on the Illumina

NovaSeq instruments, whatever applications are best run on the Illumina machines can just as readily be run on the DNBSEQ-T7 machines.

v. Other First Generation MPS Platforms

51. There are a number of other companies that are either trying to develop or have developed different first generation MPS machines. Qiagen decided to develop an integrated MPS solution that had everything from sample preparation through post-sequence analysis (they purchased the analytical company Ingenuity for their analysis platform).[44] However, they purchased the rights to a new sequencing by synthesis platform which had a number of severe limitations. The platform had very low sequence output and it had lower sequence accuracy than the Illumina platform machines. They were also successfully sued by Illumina for patent infringement, in which Illumina received an injunction against Qiagen.

52. Qiagen has recently decided to not pursue its sequencing strategy on its own sequencers, and instead has partnered with Illumina to offer kits for use on Illumina's sequencing systems. It was recently announced that Thermo Fisher hopes to acquire Qiagen. If Qiagen is successfully acquired by Thermo Fisher, and the integrated Qiagen complete sequencing solution is then based upon the Ion Torrent sequencing system, this would effectively be an integrated solution for clinical sequencing of small gene panels. Since the Ion Torrent system has a much lower sequence output than either the Illumina or BGI high throughput machines, it would not be a viable

[44] *See* Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160072.

solution of either exome, or more importantly, whole genome sequencing.

53. Genapys has developed a small desktop sequencer which is based upon an electrical-based platform utilizing complementary metal oxide semiconductors ("CMOS"). The surface of the CMOS chip has millions of sensors each one designed to capture one clonally amplified bead (of course done by emulsion PCR). The strength of this platform is the overall low cost of the small machine, and lower cost per sample to run this machine. However, it shares many of the weaknesses of the Ion Torrent platform and an even lower sequence output.

54. In response to the need for lower cost MPS technologies, a number of the companies have been producing small and inexpensive machines following on the Genapsys lead. Thermo Fisher (who owns Ion Torrent) recently announced the Genexus integrated sequencing system, which claims to be able to take a clinical sample to useful targeted sequencing data in less than a day. In addition, the Genexus system is a low-cost desktop based sequencing solution (approximately $50,000). MGI has also jumped into this fray and has now produced two small machines, one for library preparation and the second for DNB-based sequencing. These two machines together only cost $20,000. Illumina also has a small electronic sequencer (the iSeq 100) that is similar in cost and output to these other desktop machines.

vi. Problems with all First Generation MPS platforms

55. As discussed above, the strength of at least two of the MPS platforms, Illumina and BGI, is that they can offer outstanding sequence output (up to 6 and 7 Tb, respectively) and relatively accurate sequence data. However, all first generation MPS platforms, which are reliant on amplifying sequence templates prior to sequencing, are limited in that they can only generate relatively short DNA sequences (200-250 base pairs from the ends of amplified fragments). This poses severe limitations in a number of different applications of MPS. The first is that it is very difficult to generate complete whole genome sequences from complex organisms (45% of the human genome is comprised of highly repetitive sequences) with short read sequencing technologies. Second, it is very difficult with short read sequencing technologies to characterize transcripts that are produced in the transcriptome, many of which are considerably longer than the read lengths capable with short read MPS platforms. Since many transcripts have multiple transcript isoforms, it is very difficult to

determine precisely which isoform one is sequencing with short read technologies. Finally, in order to ascertain methylation across the genome with these technologies, one first has to sequence the unmodified genome and then sequence the entire genome after bisulfite modification (which turns all 5-methyl-cytosines to uracil).

D. Second Generation MPS Platforms

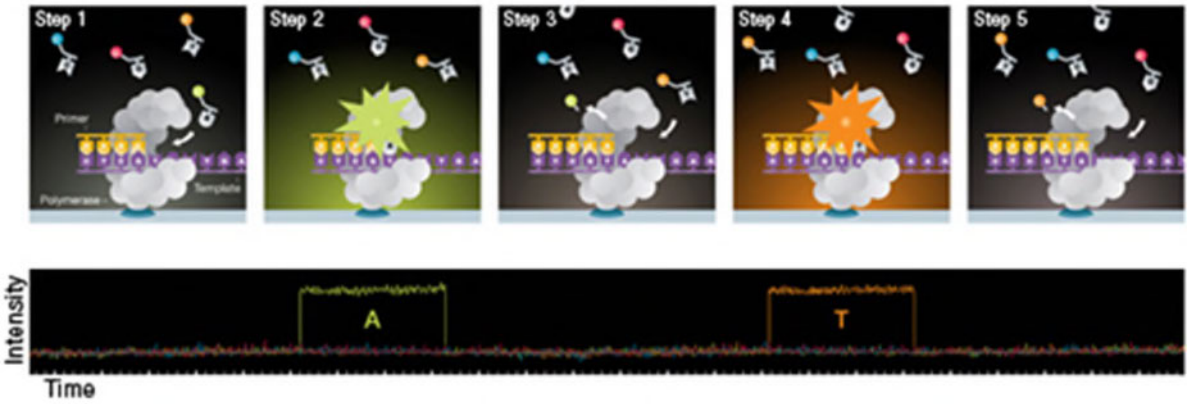
56. Second generation MPS platforms do not amplify DNA fragments prior to sequencing. Instead, they analyze single unamplified DNA molecules. These molecules can be considerably longer than the DNA fragments that are amplified for any of the 1st generation MPS platforms. In addition, the signal generated after a base is added onto these single molecules doesn't degrade after a couple of hundred base pairs as do all the signals on 1st generation platforms. As a result of this, they are capable of generating very long sequence reads, so another way to classify first and second generation MPS technologies is to call them short-read (1st generation) and long-read (2nd generation) sequencing technologies. Second generation technologies have demonstrated that they are capable of determining the sequence of DNA fragments in excess of one million base pairs (even though the average DNA sequences determined are in the 10,000 to 50,000 bp range). This makes it much easier to characterize complex genomes, characterize structural genomic changes in cancer and disease, and also to resolve transcript isoforms. Another added strength of these technologies is that they can directly resolve methylated from unmethylated bases. However, there is a cost for these long reads and that is lower sequence output than the production scale Illumina or BGI machines and lower overall sequence accuracy (which will be discussed below).

i. Pacific Biosciences

57. The first viable 2nd generation sequencing technology was developed by the company Pacific Biosciences. Pacific Biosciences detects base incorporations along single molecules by placing them into a narrow zero mode waveguide ("ZMW") with a single DNA polymerase tethered at the bottom of the ZMW.[45] Each of the four bases is labeled with a different colored fluorescent tag and as bases are incorporated the fluorescent tag is released and this can be detected from the top of

[45] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160074, ILMNBGI0160079-ILMNBGI0160080.

the ZMW with a CCD camera, as is shown in the figure below.

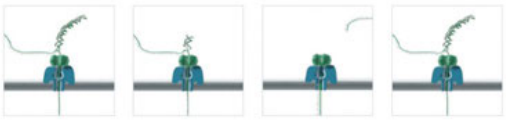


58. The strength of this platform is that it can generate long sequence reads and can also generate that sequence relatively rapidly. However, the overall sequence accuracy on this platform for a single read is only 85%, as many base incorporations are simply missed. Fortunately, the errors that this machine makes appear to be sequence independent so one solution to generate higher overall sequence accuracy is to sequence the same fragment multiple times. This is accomplished by ligating oligonucleotides which form hairpin loops (which are called Smart Bells by Pacific Biosciences) at the ends of fragments which enable fragments to be circularly sequenced multiple times. The resulting consensus accuracy after 4-5 passes gets closer to 99% sequence accuracy. There have been a number of advances on this platform over the past 10 years, and the current generation of these machines (the Pacific Biosciences Sequel II) is capable of running chips that contain 8 million ZMWs which are capable of generating up to 4 million high fidelity reads which are 10 Kb in length for a total sequence output of 40 Gb. This output is still considerably below what can be obtained on either the Illumina or BGI machines, and at a slightly lower overall sequence accuracy, even with the high fidelity resequencing reads.

ii. Oxford Nanopore

59. As its name suggests, the Oxford Nanopore sequencing platform is based upon the utilization of nanopores and how DNA molecules threading through biological nanopores changes the electrical conductance across that nanopore which can be measured.[46] The basic sequencing unit for all Oxford Nanopore machines is the MinION which is a small hand-held device (shown below).

[46] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160074, ILMNBGI0160079-ILMNBGI0160080.



60. Contained within this device are the biological nanopores and long DNA molecules are threaded through the nanopore with the enzymatic assistance of a motor protein. As the DNA molecules go through the pore, they change the electrical conductance on both sides of the pore and that can be translated into the sequence of the nucleotides going through the pore.[47] However, there are usually 6 nucleotides present within the pore at any one time. Determining the precise six-mer that is present within the pore at any one time is difficult, and, as a result, the Oxford Nanopore only has at best a 90% first-pass sequence accuracy. Oxford Nanopore has made some dramatic improvements in the past few years dramatically increasing its overall sequence output, but it is still a fraction of what can be obtained with 1st generation MPS technologies. They have higher throughput machines which effectively run multiple (up to 48) MinIONs in parallel, and the output on these machines has increased and now is multiple Tbs per run. However, one cannot correlate sequence output on these machines directly to those obtained on Illumina or BGI machines because of the lower overall sequence accuracy on the Oxford Nanopore platform.

61. Similar to Pacific Biosciences, Oxford Nanopore is also capable of reading very long sequences and has reported obtaining read lengths in excess of 2 million base pairs. This was done by a team at the University of Nottingham in the United Kingdom, and the full read length was 2,272,580 bases in length. The ability to generate such long read lengths can thus facilitate complex genome mapping, and determining transcript isoforms. Similar to Pacific Biosciences, the Oxford

[47] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160079-ILMNBGI0160080.

Nanopore can resolve cytosine from 5-methyl-cytosine, so it too can directly measure DNA methylation.

E. Ultra-High Throughput Sequencing

i. Illumina and Ultra-High Throughput Sequencing

62. In their 2016 Executive Summary, Illumina first described two new sequencing platforms that they were working on called Voyager and Firefly.[48] Firefly was their electronics-based sequencing platform, which ended up becoming their small desktop iSeq 100 system (which is capable of generating 1.2 Gbs of sequence data). Voyager was Illumina's high-throughput platform. In their report, they describe Voyager as a factory-scale sequencer capable of producing [redacted] of sequence output, and by 2019. In their 2017 Executive Summary, Illumina discussed their roadmap towards even higher sequence output and their plans to have the capability of the Voyager platform machines that could generate [redacted] of sequence output per run.[49] The Voyager platform was released as the NovaSeq, and the highest output chips that are currently made for that platform are capable of generating 6 Tbs of sequence output (20 billion reads on two flow cells). With the NovaSeq 6000 and the high output flow cells the sequencing cost for generating 100 Gbs of sequence (which is sufficient for 30X whole genome sequencing) is potentially just $475 (at a discounted price). The NovaSeq 6000 began shipping in March 2017. Currently, the NovaSeq's output remains at 6 Tbs with no further increases in three years since its release.

ii. BGI and Ultra-High Throughput Sequencing

63. All BGI sequencing machines utilize the techniques developed by Dr. Drmanac and co-workers at Compete Genomics, which was purchased by BGI in 2013. Prior to this purchase, BGI was one of the largest purchasers of Illumina high throughput machines, and their high-throughput sequencing capabilities rivaled those of the Broad Institute in Cambridge, MA. Once BGI purchased Complete Genomics, they began to shift their sequencing capabilities to Complete Genomics High-Throughput sequencing machines. At the time, the highest throughput Complete Genomics machine was called the Revolocity.[50] This machine was produced to challenge the Illumina X10, which was

[48] *See* 2016 Executive Summary.

[49] *See* 2017 Executive Summary.

[50] *See* Ex. D111 at ILMNBGI1069476-ILMNBGI1069479.

10 high throughput sequencing machines, each capable of generating 1.2 Tbs of sequence output (these were actually the first Illumina machines which started to use patterned flow cells). The Revolocity had a robotic arm in the middle of a group of sequencing machines (all using Complete Genomics-based technologies) and was supposed to be capable of also generating at least 10 Tbs of sequence output per run. However, shortly after BGI purchased Complete Genomics they announced the discontinuation of the Revolocity (along with the laying off of a number of Complete Genomics employees). BGI started producing smaller output sequencing machines utilizing Complete Genomics Technologies. A few years later the manufacturing arm of BGI (which was called MGI) started to make different sequencing machines with different sequence outputs. However, none of these had capabilities similar to the factory-scaled Revolocity sequencer.

64. On the highest throughput MGI machines that BGI was then producing, they started to sell 30X WGS in 2018 for the full cost of just $600, which was considerably cheaper than the comparable cost on Illumina machines. This sequencing, however, required users to send samples to BGI for sequencing and post-sequencing analysis for customers. Recently, BGI announced that they had reduced this cost to just $400, also as part of their next generation sequencing service. This reduced cost whole genome sequencing is done on the MGI DNBSEQ-T7 or higher throughput machines.

65. Last month at the Advances in Genome Biology and Technology ("AGBT") conference, Dr. Drmanac announced a new ultra-high throughput sequencing platform which can produce 30X whole human genome sequencing at $100 in consumable costs when running at scale. This new sequencer, the DNBSEQ-10x, can be custom ordered for high-throughput sequencing facilities.[51] This custom system (shown below) will have 7 Tb of sequence output per a 3.5-day run, more than any output currently available on any Illumina sequencer.

[51] Ex. D13 at 2.

66. The DNBSeq Tx shares many of the features of the Revolocity system including the robotic arm in the middle of the system and a modularized system for sequencing multiple slides. However, the DNBSeq Tx integrates four high-throughput imagers (compared to one in Revolocity) with a new type of shared slide dipping fluidics with better utilization of reagents and has dramatically increased the overall sequence output per run, and as a result can offer high throughput technologies like whole genome sequencing at an even lower overall price. This system has an output of 70 Tbs per run, or 20 Tbs per day, and a run time of 3.5 days. It processes up to eight independent slides, each of which can produce data for up to 150 human genomes at 30X coverage. The Tx slides are four times bigger than the flow cells for the T7, and the DNBs are packed at twice as densely on the arrays than the T7 arrays. A single DNB Tx system can thus generate up to 100,000 30X whole genomes per year. This system also has considerable headroom for improvement, as reducing the diameter of the DNBs to 100nm instead of the 200 nm current used is definitely possible. This is due to the very strong signals from the antibodies used in the chemistry, which would then allow for the DNBs to be packed even more densely on the array. With these capabilities, BGI has the potential to develop factory-scaled sequencing machines that could generate 100 Tbs and greater sequence output per run. It should also be mentioned that a in research article published by Dr. Rade Drmanac and colleagues demonstrated highly accurate sequencing with DNBs that comprise only 50 template

copies, thus a system utilizing such small DNBs could potentially generate 200-400 Tbs of sequence output.[52]

F. Uses of MPS-based Technologies

67. All MPS technologies are capable of determining the sequence of DNA molecules. What precisely is sequenced on any MPS machine is entirely up to the user and can vary from the comprehensive examination of the entire genome sequence (which is referred to as whole genome sequencing, or WGS), down to small defined portions of the genome (targeted sequencing). RNA molecules can also be sequenced (either by converting it into cDNA and then characterizing these molecules with 1st generation MPS technologies or directly with 2nd generation MPS technologies), which is referred to as RNAseq (or transcriptome sequencing), and DNA methylation can also be characterized with these technologies.

i. Whole Genome Sequencing ("WGS")

68. The most comprehensive way to examine an organism (and that organism can vary in size from the smallest bacteria, to humans, or to some of the highly complex plant genomes, which are even larger) is WGS.[53] In order to do WGS on an organism, one must first isolate DNA from that organism and fragment it into the proper size depending on which sequencing machine the samples are being analyzed the samples on. Generating libraries for WGS analysis is one of the easiest of the MPS libraries to make. Depending upon the size of the organism will help you to determine how much sequencing is required for full WGS. It is generally assumed that it takes about 100 Gbs of sequencing (with the accurate 1st generation sequencing capabilities of Illumina or BGI) to characterize the 6 Gbs human genome. However, if the scientist is analyzing a heterogeneous mixture of genomes (which can be observed in some cancers) more sequencing may be required. The standard amount of WGS required for regular whole genome sequencing gives approximately 30-fold coverage of the entire genome and is thus called 30X WGS.

69. While the cost of generating 100 Gbs of sequence data on the Illumina NovaSeq or BGI T7 machines is now less than $500, that is not the full cost of WGS. The full cost of WGS

[52] D.N. 12-39 at 1.

[53] Ex. D108(ILMNBGI0160068- ILMNBGI0160086) at ILMNBGI0160082.

includes the cost of DNA isolation and library preparation (approximately $100-200), the DNA sequencing, post-sequencing data analysis, aligning that sequence against the reference genome, interpretation of the results, and the cost for storing that data. There are a variety of sequence providers that will provide 30X WGS and the costs they charge vary between $149 per sample (Veritas) to $5,000 per sample (Illumina Clinical WGS).

70. BGI is attempting to make their mark in the WGS space and for the past year have been charging just $600 for 30X WGS (100 Gbs of human DNA sequencing). However, this still requires customers to send samples to them and for them to do the sequencing on their machines. They recently announced that they were lowering this price further to $400, and this is significantly less than Illumina-based sequencing.

ii. Whole Exome Sequencing ("WES")

71. A much easier alternative than WGS to characterize genome-wide alterations is to analyze just the transcribed portion of the genome, which is the sequencing of the exome.[54] The human exome is approximately 38 Mbs in size, which requires considerably less sequencing than the entire genome. However, it is first necessary to purify the 200,000 exons from the rest of the genomic DNA. The best strategy for this was first developed by scientists at the Broad Institute and utilized by Agilent as part of their SureSelect protocols. Oligonucleotides complementary to each of the sequence targets (in this case individual exons) are synthesized on microarrays. The oligonucleotides are released from the microarray surface and then they are all converted into biotinylated RNA which act as baits for the capture of sequences of interest. Genomic DNA is isolated from the individual and is fragmented into 300 bp pieces. These pieces are end-repaired and ligated with both sequencing and PCR-compatible primers. The biotin-labeled baits are then hybridized with the genomic DNA and sequences of interest are captured using streptavidin-coated magnetic beads. The captured DNA is PCR-amplified and then directly sequenced. There are a number of advantages of WES over WGS, including the lower cost, as there is much less DNA to sequence and analyze, and much less data to store over time. However, one decided disadvantage of WES is that if the alterations that are responsible for what the scientist is analyzing are outside of the exome, they will not be detected by

[54] Ex. D108 (ILMNBGI0160068-ILMNBGI0160086) at ILMNBGI0160082.

WES. The Figure below shows how sequence capture is accomplished.

72. WES can best be performed on Illumina or BGI-based machines. However, it can also be done with the Ion Torrent GeneStudio S5 system. WES is not a good technique for any of the 2nd generation MPS technologies as most of the actual exon targets are only around 100-200 bp in size.

iii. Smaller Gene Panels

73. For many clinical applications, WGS, or even WES, is simply way too much sequencing. Indeed, currently the most utilized form of MPS is for targeted small gene panels. Depending upon the number of genes that one is interested in examining, they can be isolated via hybridization (as is done for WES) or for a smaller number of targets with multiplexed PCR. The advantage of these smaller targeted gene panels is that they only focus on the genes of interest, so there is less sequencing, data analysis, and storage costs associated with this approach. However, only the genes that are on the targeted panel will be sequenced. Another disadvantage of this approach is that the clinic needs to run lots of different types of capture chips depending upon the clinical indication, so that there are far more "assays" being run. The two alternatives to a targeted smaller gene panel are: WES which offers the ability to detect alterations in genes not usually associated with specific phenotypes, and WGS which offers the ability to detect things outside anywhere within the genome. Another advantage of these two techniques is that they simplify the overall workflow, and one sequencing solution can be used for a large number of clinical applications. Smaller gene panels can be run on all of the 1st generation MPS machines, although they are cheaper when run on higher output machines. Sequences captured for small gene panels are not a good use for the 2nd generation long read technologies.

iv. Transcriptome Sequencing- RNA sequencing- ("RNAseq")

74. All of the sequencing uses described above focus on the analysis of DNA and as such do not help to determine what is actively being transcribed in specific cells. However, the transcripts that are actively being transcribed can be analyzed by first purifying transcripts present within any RNA sample from the highly predominant ribosomal RNA sequences present, and then converting the remaining transcripts into complementary cDNA sequences which can then be readily sequenced

with MPS technologies. This is called RNAseq for RNA-based MPS sequencing.[55]

75. RNAseq can be very complementary to DNA sequencing as it provides information as to which mutated genes (observed by DNA sequencing) are being transcribed. This information can be very valuable in the analysis of alterations in cancer genomes. Scientists at the Mayo Clinic have developed a clinical test based upon RNAseq to examine clinically significant fused transcripts in leukemias and lymphomas.

76. Depending upon what the scientist is hoping to detect with an RNAseq experiment can help to determine which sequencing platform is ideal for his/her needs. If the researcher is just interested in making accurate measurements of gene transcription and care less about transcript isoforms, then the best bet is the Illumina or BGI platforms.[56] They can offer the lowest cost RNAseq data. If it is important to know about each transcript that is being sequenced for accurate isoform expression, then the best bet is one of the 2nd generation sequencing technologies, even though it will cost more per sample than on BGI or Illumina machines.

v. Methylation-Based Sequencing

77. In addition to the four known bases of DNA, A, T, C and G, there are a number of base modifications that are important. The one modification is methylation of cytosine to 5-methyl cytosine and how this sometimes controls gene expression. To analyze methylation with 1st generation MPS technologies, it is necessary to first sequence the entire genome and then to sequence the same genome after bisulfite modification. If this appears to be too much overall sequencing (doing WGS in duplicate for each sample), there are a number of strategies to enrich for methylated sequences first which require less overall sequencing. The alternative to this is to directly use 2nd generation MPS technologies which can simultaneously determine both the sequence and the methylation of cytosines.

78. Currently, the cheapest way to determine genome-wide methylation in a single individual would be to send that individuals DNA to BGI for 30X WGS at a cost of $400. Then, also send that same individuals DNA after bisulfite modification for 30X WGS at an additional cost of

[55] *See* Ex. D110 (ILMNBGI1076905-ILMNBGI1076912) at ILMNBGI1076905.

[56] *See* Ex. D110 (ILMNBGI1076905-ILMNBGI1076912) at ILMNBGI1076905-ILMNBGI1076906.

$400. The same experiment on Illumina machines would run $3,000-4,000 at least. It is possible to do sufficient sequencing on either of the 2nd generation sequencing machines to get 100 Gbs of semi-accurate sequence data, but that would cost at least $4,000 as well.

G. Novel and Exciting Clinical Applications of MPS Technologies

i. Liquid Biopsy

79. One of the most exciting areas where MPS technologies is going to have a dramatic impact is the ability to detect rare mutant molecules in a sea of normal molecules. This is precisely what is observed in the blood of cancer patients. If that cancer has metastasized, there is some concentration of DNA from that cancer in the blood of that patient. The concentration of mutant DNA is then a direct indication of the amount of metastatic tumor DNA in the body of that individual. The liquid biopsy utilizes the massively parallel sequencing power of MPS to analyze for rare mutant molecules in a clinical sample.

80. For example, in the cancer that I work on, oropharyngeal squamous cell carcinoma (cancer of the base of the tongue and tonsils), patients are first surgically treated to remove the tumor. Then, a few weeks later they start a course of chemotherapy, followed by a course of radiotherapy (which together can cost up to $500,000). Except for the surgeon checking to make sure that they got most of the tumor that they could get in one patient, there is no way to know: (1) if the surgery successfully removed all of the tumor; and (2) if it didn't when are those residual cells starting to grow back.

81. This all changes with the liquid biopsy as scientists can analyze the blood of the cancer patient a week after surgery and, if all the tumor was removed in the surgery, we will know as there will be no residual mutant DNA detected in the blood from that patient. That patient will not have to undergo the painful and costly procedures of chemotherapy and radiotherapy. For those patients where the surgery did not remove all the residual tumor, the liquid biopsy is a rapid and accurate assay for clinical tumor growth in those patients. We can also more directly monitor an individual patients' tumors direct response to different therapies.

82. The liquid biopsy is proving to be a very effective way to monitor patients during their therapies and it is anticipated that we will start seeing this approach used in the clinic more and more

over the next few years.

ii. Early Cancer Detection

83. One more area where MPS technologies are going to completely transform things is in the area of early cancer detection. MPS technologies were first used to characterize the genome wide alterations in large numbers of different cancers. Today, several thousand cancer genomes have been completely analyzed with WGS, and also a number of other complementary "omics" technologies. This has helped to define the actual targets of different cancers.

84. This information will then help to identify molecular markers for the early detection of different cancers. For most cancers, the earlier that they are identified, the greater the patient survival, thus this offers the ability to dramatically change how we deal with the problem of cancer. In addition, a sufficient number of WGSs performed on a large enough group of people will help us to identify molecular markers out of whole genome data that would tell us whether an individual was more or less predisposed to different types of cancer. Thus, WGS could lead to better stratifying of individuals with respect to their risk of different diseases.

85. A company that was developed from Illumina, Grail, has now focused their efforts on using Illumina sequencing to detect early cancer mutations out of biological fluids (such as blood or urine), and this would aid in detecting cancers when they are much smaller and treatable.

86. It may not be necessary to always utilize MPS technologies for early cancer detection. I worked with scientists at the Mayo Clinic to help to develop the Cologuard test for the early detection of colorectal cancer (which is now sold by the company Exact Sciences). This is a test which is dependent upon a number of molecular markers, including methylation of certain targets and a mutational hot-spot in the K-ras gene which can be detected with PCR-based methodologies. However, MPS technologies frequently are the first step towards identify potential mutational targets, which can then frequently be monitored with non-MPS technologies.

iii. Microbiome Sequencing

87. The massively parallel sequencing capabilities of MPS technologies also make them ideal for the characterization of hundreds, or thousands of different genomes coinhabiting the same space. The mixture of microorganisms present in a variety of different samples can be readily

analyzed by simply isolating total DNA and subjecting it all to DNA sequence analysis. The sample can be human stool, urine, blood, skin, from livestock, or from important crops. What is important is that the mixture of different microorganisms in different samples will be useful for determining the overall "health" in that sample.

iv. Other MPS Applications

88. The applications of MPS technologies listed above are not even a small fraction of the different uses that this powerful technology is going to have, not just to scientists and not just in the clinic.

H. Clinical and Research Uses of MPS Technologies

89. The three major areas where MPS technologies are utilized are (1) in a research setting, (2) in a clinical setting, and (3) in agriculture and animal husbandry. Traditionally, things are discovered in a research setting and then those with clinical relevance are developed into assays in the clinical setting. The only step that is changing is that the power of sequencing technologies greatly decreases the amount of time from discovery to clinical or agricultural application.

i. MPS in Research

90. Determining which MPS platform is best suited for work depends on the desired result or outcome that the scientist is are trying to get from the experiment. However, most MPS technologies in academic institutions are not housed in any one individual's laboratory. Most research institutions that have invested in MPS technologies have done this within Research Core Facilities so that a single research Core can try to cost effectively meet the myriad of research needs from their community. The problem is that no one sequence instrument or platform can meet all the needs of such a diverse group. A customer would need high throughput 1st generation machines for WGS and WES experiments, at least one of the 2nd generation platforms up and running for experiments requiring the power of long read technologies, and most likely a variety of the smaller inexpensive machines that are useful when there are only a few samples for examination.

ii. Clinical MPS

91. The most frequent application of MPS today in the clinic is its utility for running small gene panels. There are a variety of commercially available kits for specific sets of selected genes although many places are simply developing their own targeted gene capture panels. As with all MPS

technologies, more than 90% of these are also being done on the Illumina sequencing platform. Pl.'s Mot. Preliminary Injunction 19-21.

92. In the Neonatal Intensive Care units ("NICU"), thanks to the pioneering work of Dr. Stephen Kingsmore and colleagues, they have developed techniques for rapid WGS on patients where they can obtain and analyze the data from one patient, and their parents in less than 24 hours. This dramatically changes the long and sometimes quite arduous process of the diagnostic odyssey to identify the underlying causes of clinical problems that are frequently observed in the NICU. This pioneering work has led to a change in thinking at other NICU units and this approach may quickly become the one of choice. WGS is also being using to study patients with rare diseases. Other than these two instances there is limited clinical WGS being routinely done, and just about none in the clinical treatment of cancer patients.

93. As previously mentioned, one of my colleagues, Dr. Kevin Halling, recently developed a clinical MPS assay based upon RNAseq to detect novel gene fusions in leukemias and lymphomas. Another of my colleagues, Dr. George Vasmatzis, has developed another clinical assay based upon the novel technology of mate-pair next generation sequencing which is a technique to examine and sequence the ends of much larger stretches of DNA for the characterization of chromosomal abnormalities. The Mayo Clinic is currently evaluating mate-pair sequencing as an alternative to either classical cytogenetics or the more molecularly oriented array comparative hybridization.

iii. Population-Based WGS

94. One of the most significant uses of MPS technologies over the next several years will be the large population-based WGS that are being planned in different countries. The National Health Service of the United Kingdom is working with Genomics England and they are biobanking DNA from 5 million UK individuals. They already have plans to perform WGS on the first 500,000 of these in the next three years with further plans to sequence all 5 million. The major goal of this work is to demonstrate the utility of such an approach to develop a truly Personalized Medicine approach to patient care. A similar effort in the United States is the All of Us Project that is collecting samples from 1 million Americans prior to most likely also doing WGS. Similar projects are underway in

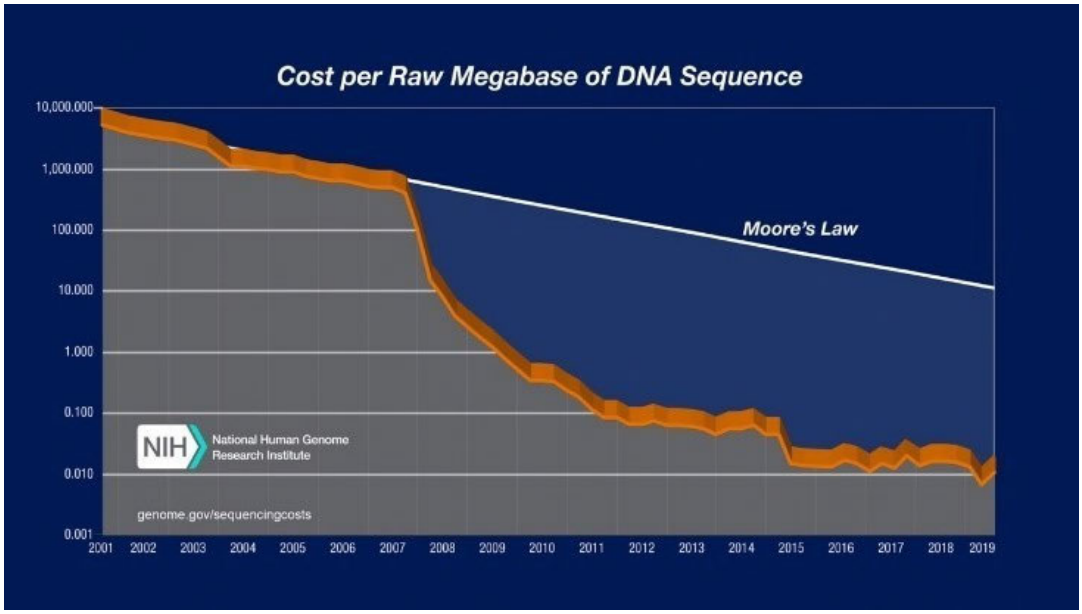
China, and a number of other countries. Eric Greene, the head of the National Health Genome Research Institute, and Ewan Birney (the director of the European Bioinformatics Institute) both estimate that over the next 5 years there will be a total of 50 million individuals who have had their genomes completely analyzed by WGS.

iv. WGS As A Routine Part of Health Care

95. As stated, the goal of the project underway by Genomics England is first to obtain whole genome sequence data on a large enough group of individuals from the United Kingdom to get a better picture on the variations in DNA sequence that are present within their population. The real goal, however, is to determine whether or not WGS could play an important part of maintaining the health of individuals, and transform that way that the National Health Service takes care of the people of the United Kingdom.

I. Price Points for the Accelerated Adoption of Different MPS Technologies

96. The cost for doing a specific MPS application decreases as the sequence output on MPS machines continues to increase. It is useful to review what happened with increased sequence output and the adoption of RNAseq to measure gene expression as compared to its predecessor, microarray-based gene expression measurements. By the time MPS technologies were starting to be developed, microarray-based gene expression experiments had reduced their cost to only several hundred dollars per sample. As long as RNAseq was considerably more expensive than microarrays for gene expression, there was little research adoption of RNAseq, even though RNAseq data was vastly superior to data obtained with microarrays. However, there was a point at which sequence output became so great that suddenly the cost for RNAseq also dropped to just a few hundred dollars. At that moment, there was a massive adoption of RNAseq as the assay of choice for measuring gene expression. It was not a linear relationship, but instead a sudden and dramatic moment where the price point lead to the accelerated adoption of this superior technology. This was greatly facilitated by the availability of the first HiSeq 2000 machines. The graph (below) shows the decreased cost in sequencing (per megabase of sequence data obtained) over the past 20 years, since the first draft sequences of the human genome were generated with CE-based sequencing.



97. There are a number of key messages within this graph which are important to realize. The first is that the first major decrease in the overall cost of sequencing was a result of the development and improvements on the 454 sequencing platform. The most impressive part of this curve, however, occurred between the end of 2007 and 2011 and is totally due to improvements on the Illumina sequencing platform, especially as a response to Complete Genomics $5000 30x human WGS. While the original Genome Analyzer could only produce about a Gb of very short sequence data, by the time of the introduction of the HiSeq 2000 machines (in 2011) the Illumina platform was capable of producing 200 Gbs of 150 bp-plus sequences. This is a 200-fold improvement in sequence output and a corresponding 200-fold decrease in the cost per Mb of DNA sequencing.

98. In 2011, Illumina claimed that their HiSeq 2000 machines had exceeded the need for increased sequence output, but in reality what occurred was that Illumina had no competition in the MPS space. There was a lull in the amount of sequencing reagents that people were purchasing from Illumina, as for a brief moment the output of the machines was greater than the demand. Then from 2011 to 2015, there were no major decreases in the cost of sequencing on this platform. Atthat point in time, the 454 sequencing platform was discontinued as its sequence output was a decreasing fraction of what could be obtained on the Illumina sequencing machines. During that period of time, a second competitor of Illumina (the SOLiD sequencing platform) also folded. The Ion Torrent platform started in this time period, but due to the limited sequence output on that platform, it offered

no real competition for Illumina for the important analysis of whole genomes.

99. The only time there was a further drop in the sequencing cost per megabase was in 2015, which coincided with BGI announcing that they were making and selling sequencing machines based upon DNB amplification of templates. Indeed, since 2015, there has been no major further decreases in the overall cost of WGS on the Illumina platform.

V. A PRELIMINARY INJUNCTION IS AGAINST THE PUBLIC INTEREST

A. The Public Interest Favors Access to BGI's Sequencing Technology That Has Several Important Advantages Over Illumina's Sequencing Technology

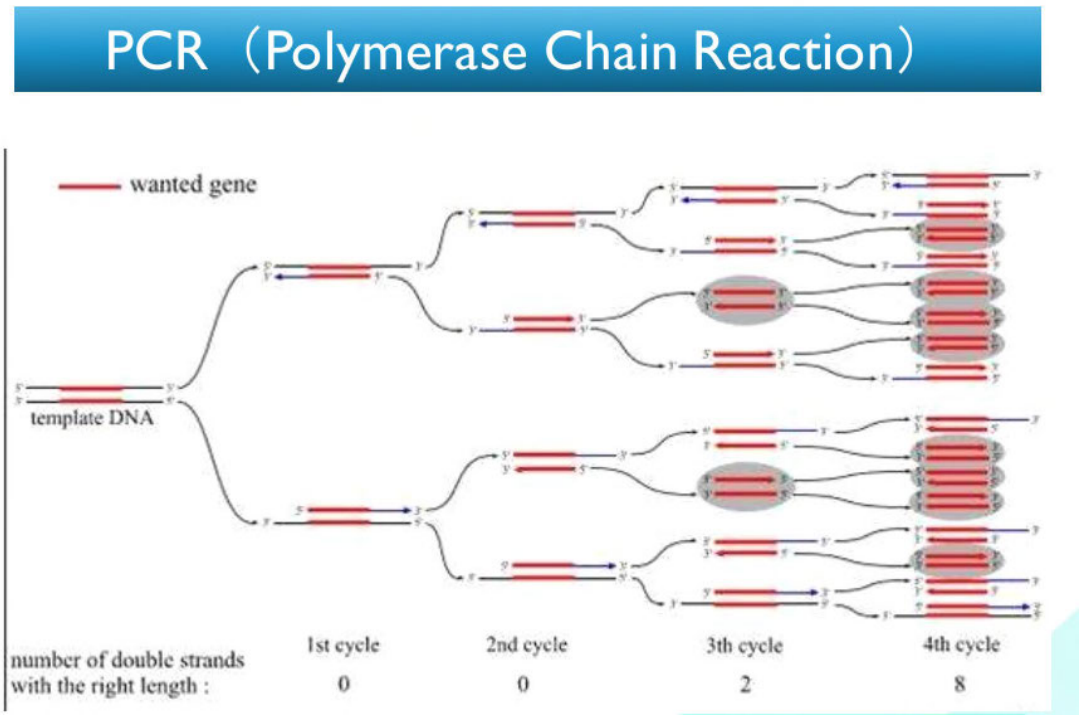
100. Much of what I have described above focused on how BGI sequencing is comparable to Illumina sequencing, and how these two methods offer both choice to the user. Both are excellent for high-throughput short read sequencing technologies. They are both highly accurate sequencing technologies, when compared to long-read second generation MPS technologies. However, there are inherent advantages to the BGI-based sequencing as compared to Illumina-based sequencing.

a. BGI's DNBSEQ Methods Use Linear Amplification, Which Has Advantages Over Illumina's Bridge Amplification Method

101. The first advantage is the BGI machine uses DNB-based sequencing, which does not utilize PCR to amplify individual molecules, as does the bridge amplification method used by Illumina. This advantage applies to both the StandardMPS and CoolMPS sequencing reagents.

102. One of the major problems with PCR amplification is that it is based upon making copies of copies , which means that any error is reproduced many times over. This problem is due to the fact that all polymerases have an inherent error rate and any sequence changes that occur early within the amplification process end up becoming a substantial part of the final population of amplified DNA fragments, as PCR makes copies of previous copies. This problem is depicted in the image below, where the grey ovals represent where an error occurred.[57]

[57] D.N. 12-19 (Van Oene Decl., Ex. S) at 21.



103. One area where errors due to Illumina's use of PCR for amplification can be a substantial problem is when multiple samples are mixed together into a single sequencing lane. The way amplified fragments from different individuals (or samples) are resolved is through the use of short DNA sequence bar-codes that are ligated to the ends of the fragments. Errors in the PCR amplification process can cause changes in the sequences of the bar codes, and this results in amplified fragments from one individual possibly being confused with those of another.

104. In contrast, BGI uses a linear amplification process, which does not have this problem because the amplified copies are each derived from the original DNA fragment, rather than copies of the original DNA fragment. As a result of using linear amplification, there is a much lower error rate in the linear amplification process that BGI utilizes. This results in much less bar-code confusion with the BGI sequencing method.

105. Illumina's documents reflect its awareness of this issue. In one of Illumina's internal presentations regarding BGI, it identifies BGI's claim of "[redacted]"[58] The same slide identifies BGI's claim

[58] Ex. D48 (ILMNBGI1085299) at ILMNBGI1085319.

of [redacted]"[59] The use of DNB amplification is still superior to dual indexing and demonstrates that Illumina is quite aware that there are reasons why linear amplification are superior to PCR-based methodologies.

b. BGI's DNBSEQ Linear Amplification Approach Requires Fewer Copies of the Template, Thereby Reducing Use of Costly Reagents

106. BGI's DNBSEQ linear amplification method requires fewer copies of the individual template being sequenced, and therefore requires less of the consumable sequencing reagents to sequence the amplified template. This advantage applies to both BGI's StandardMPS and CoolMPS chemistries.

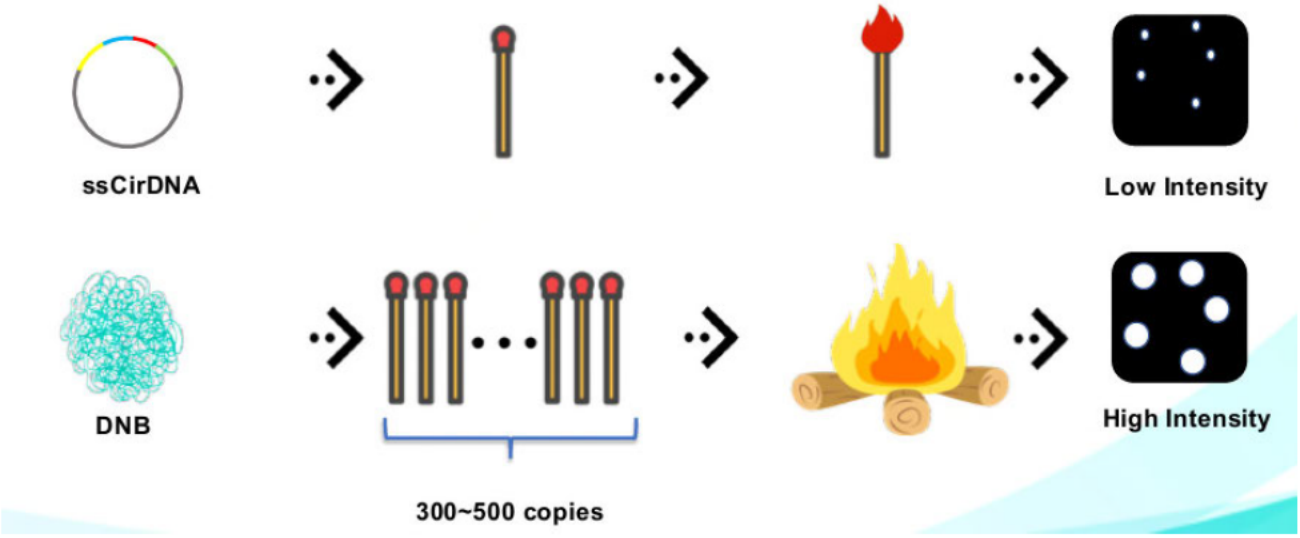
107. Bridge amplification results in the amplification of individual templates to 30,000 copies. In order to sequence these amplified templates it takes sufficient fluorescently labeled nucleotides in each step of the sequencing process to extend each of those 30,000 copies of the template. In contrast, BGI's DNBSEQ method linearly amplifies each template to just 300 copies, so a 100-fold fewer nucleotides are required per cycle to extend each of the linearly amplified copies. Over the course of numerous cycles, this has the potential to result in a significant decrease in consumable reagents.

c. BGI's CoolMPS Chemistry Has Brighter Signals That Result in Advantages in Read Length and Error Rate

Even though BGI's DNBSEQ linear amplification method requires 100-fold fewer template copies, because the Cool MPS chemistry permits use of multiple fluorophores on each antibody, without impeding the sequencing process, it still provides a sufficiently intense signal for nucleotide detection and differentiation. Indeed, the signal is sufficiently intense to get a signal that has a comparable overall sequence accuracy as the Illumina systems. Because Cool MPS does not result in leaving a residual scar after the removal of the fluorescently tagged nucleotides, there really is an expanded possibility for further increases in sequence read length. In the article describing Cool MPS they have demonstrated that they can use this technology to generate up to 400 bp reads. Since the fluorescently labeled antibodies contain multiple fluorescent groups per antibody, the ability to generate accurate sequence with much smaller DNBs (down to 50 nm) means that by cloning DNA

[59] *Id.*

fragments that are four times longer than what is currently used they could potentially do even longer sequence reads on this platform.



D.N. 12-20 (Van Oene Decl. Ex. T) at 11.

d. BGI's CoolMPS Chemistry Has Brighter Signals That Result in Advantages to Throughput

108. CoolMPS's ability to use higher intensity signals means that BGI will be able to get even greater sequence output merely by decreasing the spacing of their patterned flow cells, thereby further improving throughput and lowering cost. This inherent advantage means that BGI has significant room to further increase throughput with its current CoolMPS sequencing chemistry as it is developed further, whereas Illumina appears to have has less room for improvement with its current chemistry.

e. BGI's CoolMPS Chemistry Permits Use of Less Sequencing Reagents, Which Lowers Cost

109. Also, because the signals from BGIs CoolMPS chemistry are sufficiently strong even with fewer template copies, this novel approach will permit further reduction in linear amplification of the template, which will lead to further reductions in reagent usage, and lead to reduced sequencing costs for BGI sequencing as compared to Illumina.

B. BGI's Sequencing Products Would Provide Much Needed Choice In the Market, Which Is In the Public Interest

110. In my experience as a consumer of both equipment and reagents for biological research, and in my role surveying the sequencing market for my publications, I have observed the

negative effect that lack of consumer choice has had on the sequencing market.

111. In my 35 years of running my own research laboratory, I have found that it is always desirable to have a choice when it comes to vendors. Of course, having a choice of vendors gives consumers some degree of leverage to get the best deal possible, but the importance of consumer choice is not limited to the issue of price. Without competition, the pace of innovation stagnates and customer service suffers. In my experience in the sequencing industry, Illumina's dominance in the market (particularly for high throughput sequencing, where there are no alternatives in the U.S.) has led to reduced innovation, higher prices, and consumer frustration. Below I describe several case examples to illustrate these issues with lack of consumer choice.

a. The Mayo Clinic Experience

112. I have been involved with Illumina and their interactions with the Mayo Clinic since 2008. I wrote a proposal to the University of Minnesota and Mayo Clinic partnership in 2008 and was awarded funds to obtain the first generation Illumina MPS machine, the Illumina Genome Analyzer. Since then I continued to work as a liaison between Illumina and the Mayo Clinic, thus I feel very qualified to talk about the experience that the Mayo Clinic has had with Illumina over the past 12 years.

113. While there is simply too much history to discuss it in detail here, I can give two examples of how poorly Illumina has treated the Mayo Clinic. These experiences are not unique to the Mayo Clinic as many of my colleagues at other institutions have had similar experiences with Illumina.

114. In 2010, Illumina came to the Mayo Clinic with a whole genome sequencing proposal that initially looked very promising. At this point in time the sequence output of the original Genome Analyzer had increased from one to 80 Gbs, but it was still quite expensive to consider doing 30X WGS on multiple samples. This is because it would require both multiple machines (as it would take one machine almost 2 runs to produce enough data, and each run took 2 weeks). Since the Mayo Clinic was not about to purchase 5-10 Genome Analyzers (this would have cost over 6 million dollars), Illumina made a proposal for the sequencing of 100 genomes. In this proposal Illumina would provide the Mayo Clinic with 10 Genome Analyzers and the necessary reagents to do 30X

WGS on 100 genomes. The Genome Analyzers would be on loan and the total cost of this deal was 5 million dollars (which at that point in time looked quite good). What Illumina did not tell us what that the very next month they were planning on releasing the Illumina HiSeq 2000 machines which had 2 and ½ times the output of the Genome Analyzers and had we taken the proposed deal, we would have been paying much more for the sequencing than necessary. Fortunately, the Mayo Clinic was unwilling to spend the 5-6 million dollars at that point in time, so we avoided spending our scarce funds on outdated technology.

115. This is in stark contrast to our dealings with other MPS providers at the time (namely 454 and the Solid sequencing systems), where these providers told us about their future plans and worked with us much more as collaborators that had a genuine interest in providing us with their most advanced technology and helping us ensure that our limited funds were well-spent.

116. Over the past 12 years I have also had multiple interactions with Illumina with respect to instrument and consumable purchases. These experiences revealed that Illumina is generally unwilling to provide any substantial discounts on either machine purchases or consumables, though I understand that it does so for much larger genome sequencing centers that spend considerably more on sequencing. This leads to the unfortunate result that institutions such as the Mayo Clinic are held back in their ability to perform important genetics-based research, and this effect is even more pronounced for smaller institutions with lower sequencing volume.

b. The University of Toronto Experience

117. I have reviewed documents regarding the a recent purchase of a BGI sequencer by the Guttman Lab at the University of Toronto. This lab already had two Illumina sequencing machines and sought to purchase a BGI sequencer.[60] The lab originally sought to purchase the BGI sequencer through an "Advance Contract Award Notice," meaning that other vendors were put on advance notice of the University's intention to award the contract to MGI.[61] The ACAN specified the reasons why BGI's sequencers were being pre-selected:[62]

[60] Ex. D54 at 1-2; Ex. D73 at 56.

[61] Ex. D54 at 1-2.

[62] *Id.*

Limited Tendering Justification:

MGI Americas ("MGI") has established a technology called DNBseq that is utilized by the MGISEQ-2000 sequencer. DNBSeq uses rolling circle replication to generate copies of the original nucleic acid template, avoiding PCR-amplification induced error. The MGISEQ-2000 has the following unique features that the Guttman Lab requires for their research:

- Library preparation and sequencing is via DNA Nanoballs (DNBs). DNBseq™ provides the foundational chemistry for sample preparation
- The MGISEQ-2000 employs patterned nano-array flow cells for sequencing. There are two flow cell configurations for added flexibility
- A single DNB will attach to an arrayed spot on the flow cell via electrostatic forces thus preventing cross-talk of signal
- No clonal amplification occurs on the flow cell, thus eliminating occurrence of clonal errors and sample misidentification (index hopping)

118. Illumina protested, and the University rescinded the award to BGI and issued a Request for Public Proposal.[63] However, the RFP included the specific technical requirements that the lab found advantageous in BGI's sequencer, including use of linear amplification (as described above), and provided reasons for this requirement:[64]

> The Guttman lab sequences complex biological samples composed of a diverse range of microorganisms. Analyzing genome sequence data from a complex biological community is a powerful way to infer the composition, function, and significance of the organisms in that community. The interrogation of these samples requires next-generation (i.e. massively parallel, high-throughput) genome sequencing technology. One, long-standing limitation in the analysis of these communities is the ability to distinguish nearly identical organisms based on their genetic sequence, e.g. when attempting to distinguish very closely related bacterial clones coexisting in the same environment.
>
> The Guttman lab currently uses a genome sequencer that uses exponential template amplification and is seeking to purchase a next-generation genome sequencing platform that uses linear template amplification technology, or an equivalent technology. The system should have a patterned-array flowcell to reduce signal cross-talk and index-hopping. It should be able to generate paired-end short reads and synthetic long reads. The labs work requires that the system should have a throughput (i.e. rate) capable of producing at least 200 Gigabases (Gb) of DNA sequence data per day, and an output (i.e. yield) of at least 1 billon reads / run. It should be compatible with PCR-free library preps. The Genome Sequencer should be able to process sequencing data and demultiplex data locally on the sequencer.

119. Following solicitation of proposals, the Guttman Lab selected BGI's sequencer again.[65] But rather than concede that one of its customers could want to have an alternative sequencing system available, Illumina has continued to dispute the award of the bid, undoubtedly

[63] Ex. D90 at (ILMNBGI1087714-15) at 1-2 (designated OAEO); Ex. D at ILMNBGI1087659-60 (designated OAEO).

[64] Ex. D73 at 56 (designated OAEO).

[65] Ex. D. 109 (ILMNBGI1087740) at ILMNBGI1087740 (designated OAEO).

causing distress for its customer.[66] This is just one more demonstration of how Illumina mistreats its customers, including current customers. While I can fully understand Illumina being highly competitive with its competitors, the University of Toronto is a customer of Illumina. This example highlights how difficult Illumina can make it for a customer to purchase from other suppliers, and how Illumina does not seem to care that it is harming its customer relationship in the process.

C. The Public Interest Favors Access to BGI's Sequencing Products for Genomic Research and Advancement of Personalized Medicine.

a. Benefits to Research

120. No single sequencing instrument or platform can meet all the research needs. For example, it is very difficult to generate complete WGS from complex organisms with first generation MPS platforms, which are reliant on amplifying sequence templates prior to sequencing. It's also very difficult with short read sequencing technologies to characterize transcripts that are produced in the transcriptome, many of which are considerably longer than the read lengths capable with short read MPS platforms. Further, 1st generation platforms are not useful for ascertaining methylation across the genome. WES is not a good technique for any of the 2nd generation MPS technologies as the actual exon targets are only around 100-200 bp in size. For RNAseq experiments, the best sequencing platform depends on what the scientists is hoping to detect. If he/she is just interested in making accurate measurements of gene transcription and care less about transcript isoforms, then the best bet is the Illumina or BGI platforms due to cost. However, if it is important to know about each transcript that the scientist is sequencing for accurate isoform expression, then the best bet is one of the 2nd generation sequencing technologies, even though it will cost more per sample than on BGI or Illumina machines.

121. Thus, scientist would need high throughput 1st generation machines for WGS and WES experiments, at least one of the 2nd generation platforms up and running for experiments requiring the power of long read technologies, and most likely a variety of the smaller inexpensive machines that are useful when there are only a few samples for examination. In spite of the need for multiple technologies to be a respectable Research Core facility, it is quite revealing that over 90% of

[66] Ex. D91 (ILMNBGI1087694) at ILMNBGI1087694-95 (designated OAEO); Ex. D92 (ILMNBGI1087811) at ILMNBGI1087811-22 (designated OAEO).

sequencing data is from the Illumina platforms.

122. Between Illumina and BGI platforms, the differences described above could lead to one platform to be better suited than the other, or for a lab to want to have both platforms available. I note that Illumina itself identifies differences between the platforms and workflows.[67]

b. The Advancement of Personalized Medicine in Dependent Upon Affordable High-Throughput Whole Genome Sequencing, Whole Transcriptome, and Single-Cell Sequencing

123. It is my opinion that WGS will provide invaluable information that will have tremendous utility in health and well-being. In addition, it will completely transform clinical care from the current paradigm where individuals are treated after they develop symptoms and problems to a true Individualized and Personalized Medicine approach that first identifies individuals at risk for diseases before they develop. Once symptoms do appear, WGS will also transform how patients are treated which is based upon identifying the right drug at the right concentration for that individual patient.

124. The first step in this new paradigm will be that WGS will be something that is done on every newborn, and for certain high-risk individuals will be something that is done both on the parents and the fetuses before they are born. Thus, while the sequencing of the 50 million individuals that will be done over the next five or so years appears like a great deal of sequencing (and this is something that Illumina would like to completely control and dominate), this is nothing compared to the amount of WGS that will be done every single year once this new paradigm of health care becomes a reality.

125. One of the major tenets of true Personalized Medicine is to better manage the health and care of individuals by incorporating genome information into managed Health Care. However, in order for this to become a reality, it is absolutely essential that the various Population-based WGS efforts move forward as quickly as possible. Until projects such as the one from Genomics England are able to complete their sequencing and analysis of some 5 million individuals from the United Kingdom, we will not know the validity of genome-driven medicine. These projects also need to be

[67] *See* Ex. D48 (ILMNBGI1085299).

completed before there is sufficient evidence to support incorporating WGS, and other applications of MPS, into managed Health Care.

126. However, with the total cost for WGS staying above $1,000 (as it has since 2015), it will simply take longer for a majority of these projects to be completed. In contrast, if there is competition in the marketplace because BGI is allowed to start marketing their platform outside of China, we will see the dawn of the true $100 30X WGS come much more quickly. My contention is at that price point it will be much easier for all these projects to be completed, and in much less time.

127. While it is impossible to determine precisely how much slower all this work will proceed in the absence of competition, I can estimate that allowing Illumina to maintain their monopoly on the MPS space will slow this effort by five years, if not more. If there is competition in the sequencing space, then many of these population sequencing projects will be able to be completed by 2025. The time-frame for then adopting WGS into managed Health Care could be as early as just a few short years after that. However, without competition, my estimate is that it will not be until 2030 before enough of these sequencing projects are completed to make these conclusions, and thus it will not be until the early to mid-2030's before routine clinical WGS becomes a reality.

128. The current Health Care systems throughout the world are still mired in the classical models of treating patients once symptoms develop and tends to focus much more on treating patients with the same disorders similarly. However, the sooner the population-based sequencing studies are completed, the sooner we can begin to transition to a much better approach towards managing Health Care where 30X WGS helps to make important decisions about which individuals in the population are at a greater risk of developing which diseases. Once, symptoms have developed, genome information for those individuals, will also help to devise better patient-specific treatment strategies that are tailored to those individuals with the right drugs at the right concentrations to treat those disorders.

129. True Personalized Medicine will completely transform Health Care and will result in significant overall savings as well. One of the best demonstrations of this is in how patients are treated for different cancers. In the cancer that I work on, which is oropharyngeal squamous cell carcinoma (cancer of the base of the tongue and the tonsils), patients are usually treated first with

surgery and then with radio-therapy and chemotherapy. These three treatments cost at least $500,000 per patient (and frequently more), but without any pre-selection to first identify patients who could be just successfully treated with surgery alone. We do not have sufficient molecular markers yet to determine which patients have less aggressive tumors, which would need less aggressive treatments or lower doses of radiation or chemotherapy. As a result, most patients are treated the same and then oncologists wait to see which patients benefit. Under a true Personalized Medicine approach, we would have a better idea as to which individuals are more at risk, way before cancer has developed. Possible interventions at this stage could reduce the proportion of these at-risk individuals who would then go on to develop cancer. We would further have better early detection technologies in place so that cancers are detected at an earlier, and more treatable stage. If cancer is detected, at any stage, we would also have information about what are the genes that are altered specifically in that cancer, and that would suggest Personalized treatment strategies based upon the mutational profile present in that patient's cancer. Furthermore, with powerful liquid biopsy assays in place, patients could be more readily analyzed in real-time to determine the success of specific therapeutic regimens. All of these will completely transform cancer treatment to be considerably more cost-effective, and more importantly, considerably more effective.

130. This is just the example for cancer treatment, but the reality is that real Personalized Medicine will transform all of Health Care. This will begin with an expansion of the current non-invasive prenatal tests ("NIPTs") (which currently predict the chance of certain key chromosomal abnormalities) to a more comprehensive look across the genomes of fetuses. It will extend into the NICU, so that newborns that are failing to thrive can be comprehensively tested, and then treated appropriately. Ultimately, genome sequences will provide information about ideal diets and exercise programs based upon genotype, and then the focus will be on genome-driven healthy living. Individuals will be able to be stratified into those that are at a higher risk of developing specific diseases, and with appropriate interventions to either prevent or delay those diseases. For individuals with full-blown disease, genome information will then help to define the correct treatment strategies and the proper pharmacogenomic doses of drugs to treat that specific disease in that specific individual. However, none of this can occur until the various Population Sequencing Projects have

been completed and the resulting information correlated with clinical data from the patients.

131. True Personalized Medicine will completely transform Health Care and the savings will be significant. The sooner that the various Population Genome projects are completed, the sooner we will begin to see 30X WGS becoming a part of routine Healthcare, and the sooner we will get to the vision of Personalized Medicine becoming a reality. All of this work is thus predicated upon having the cost of WGS further decrease to price points at which this comprehensive approach towards genomics is easy and affordable.

c. Innovation In the NGS Market Has Stagnated Because Illumina Faces Essentially No Competition

132. The majority of sequencing that is now done throughout the world is on Illumina sequencing machines. Illumina itself estimates that it 90% of sequencing data is generated on Illumina systems. Despite launching in 2017, the output on the NovaSeq system remains at 6 Tbs with no further increases in three years since its release. Considering the dramatic improvements that have been made in sequence output on the Illumina sequencing platform over from 2004 to 2017 (6,000-fold improvement over a 13-year period), it is quite surprising that sequence output on the highest throughput Illumina machines has not increased at all in three years. I believe that the reason for this is that Illumina felt that they had no competition, and thus were under no pressure to improve. It could also be that Illumina found that sales of the NovaSeq were underwhelming. Illumina has discussed the NovaSeq's underwhelming sales in every years' annual report to the Securities and Exchange Commission since the NovaSeqs were released. Their interpretation was that there was not greater demand for further increases in the amount of sequence generated. This is quite unfortunate as their 2017 plans to develop a factory-scale sequencer which could generate 40 Tbs of sequence output would reduce the sequencing cost of 30X WGS to just below $50. However, for Illumina to offer 30X WGS at a cost of $100 would actually require the cost of generating 100 Gbs of sequence data to be $30-40, which would require their highest throughput machines to be capable of generating almost 75 Tbs of sequence output.

d. High Throughput Sequencing Platforms Drive the MPS Revolution

133. The highest throughput sequencing platforms not only provide a path towards reducing the cost of 30X WGS to $100 or less, but actually drive the entire sequencing ecosystem. As the cost

for doing the sequencing part of any use of MPS becomes less it actually forces the cost of other aspects of the total cost of sequencing to also drop. Furthermore, once there are machines that are capable of tens and then hundreds of Tbs of sequence output per run, it also becomes possible to generate smaller MPS machines which themselves can generate larger amounts of sequence output. Hence, all applications that are dependent upon MPS become cheaper and cheaper to run. This includes whole exome sequencing, targeted genome sequencing panels, RNA sequencing and also methylation sequencing.

134. A very hot and exciting area in the genomics space is the ability to do single cell sequencing. Information provided by single cell sequencing can help to better understand the heterogeneity that occurs in different cancers and this can help to better understand the biology of cancer development. Furthermore, it could have clinical relevance as a better understanding of the different types of alterations in different cells in the same cancer could help to better devise strategies to eradicate all of those cells as part of cancer treatment.

135. Single cell genomics has a lot of other very valuable uses as well. Currently most of these are in the research, and not clinical space. This includes analyzing individual cells to better understand nerve cell typing, examining the types of brain cells and the relationships between cells during development, prenatal diagnosis and assisted reproduction, just to name just a few of its potential applications. While there are currently not clinical applications for this, once insights are generated they could very well lead to new clinical tests.

136. Unfortunately, single cell sequencing is considerably more expensive than current sequencing methodologies which rely upon the isolation of nucleic acids from a large number of cells mixed together. Today most single cell technologies simply do not reach the same sequencing depth that sequencing of bulk cells does. This is because bulk sequencing is done on the entire sample and thus requires only a single sequencing run per sample. Single cell sequencing first requires fractioning a mixture of cells down to single cells and then analyzing some number of those cells. How many of those cells needs to be analyzed to get a good indication of the different populations of cells present in a mixture? Here, instead of doing one sequencing analysis of a mixture of cells, you have to do sequencing of some larger number of individual cells, hence, the total amount of

sequencing is considerably greater. As a result, single cell sequencing is usually not done at the same depth as the analysis of a bulk number of cells. However, once the output of the highest throughput MPS machines gets great enough it then becomes possible to analyze large numbers of individual cells and to do this at much greater depth.

e. MGI's Entrance In the U.S. NGS Market Is Necessary to Enhance Innovation and Lower Prices to Increase Affordability of More Extensive Sequencing

137. Right now is a very critical time right now for NGS market. As discussed above, personalized medicine is dependent on affordable WGS. Additionally, Population-based WGS projects are starting to ramp up towards their goals of sequencing a proportion of their respective populations. As discussed above, the goal of many of these projects is to demonstrate whether or not WGS can become an integral part to a Precision Medicine approach towards managing health care. I am extremely confident that this is exactly what they will discover and this will only be the beginning of so many aspects of DNA sequencing becoming a routine part of how we live our daily lives.

138. At this moment, the only other viable first generation MPS technologies for WGS is BGI. None of the other 1st generation companies can produce sufficient sequence output to make WGS viable. Although both Pacific Biosciences and Oxford Nanopore can do WGS, these platforms have lower sequence output than Illumina or BGI (and since both have lower overall sequence accuracy) and therefore the cost is considerably greater. It would take much more than 100 Gbs of sequence data per individual for Pacific Biosciences to generate WGS data at the same sequence accuracy as Illumina or BGI, which would further drive up the cost of WGS on any 2nd generation MPS platform. Similarly, although Oxford Nanopore has improved its overall sequence output, it is still a fraction of what can be obtained with first generation MPS technologies and therefore not as cost effective as Illumina or BGI.

139. However, BGI sequencers are not yet available in key countries that will be starting population-based WGS. As a result, these population-based WGS projects are either considering or going to be done on the Illumina sequencing platform at a current cost of over $2,000 per genome since there is no alternative to Illumina sequencing. If there are no alternatives to Illumina machines for sequencing and none for at least one (or more) years, this will essentially further solidify the

Illumina monopoly on the MPS space. In addition, the cost for sequencing those 5 million genomes on the Illumina platform will be over 10 billion dollars. If even a fraction of those genomes were to be analyzed on BGI-based machines, there could be a significant savings in the overall costs of these projects. In addition, while the current cost of 30X WGS is considerably lower than it was prior to 2015, it is still high enough that it can act as an impediment to more countries deciding the start population-based WGS. If the total cost of 30X WGS was at $100 or less, we would see a much more dramatic number of such sequencing projects starting up, and the sooner this is done, the sooner everyone will be able to validate the importance of this information to managing the health and well-being of large numbers of individuals.

140. Further, I believe the $100 genome price point will prove to be game changer for WGS. Of all the technological advances that I have since 1978, none have been as important as the advances that we have seen in the last 15 years in DNA sequencing capabilities. The advances that decreased the costs of sequencing a single genome from $200 million to just $2,000 in such a short period of time have led us to the cusp of a new world where DNA sequence information can transform how we live our lives, and how we manage the health of our populations. However, as described above, there has been no major further decreases in the overall cost of WGS since 2015. I believe this is primarily due to the fact that Illumina has not felt that there is a major competitor in the sequencing space, not because further increases in sequencing output are either not possible or not needed.

141. If the price stays at $2,000, rather than quickly dropping below $100, we will not start that explosion in WGS that will occur for a much longer period of time and will further delay the adoption of WGS-based health strategies and the true dawn of a real Personalized Medicine future.

142. While the $100 price point is most likely not be the full cost of WGS due to the cost of storing WGS data and the cost of analyzing and explaining the data, we will see an incredibly accelerated adoption of WGS as a primary clinical assay as the cost for isolating DNA, generating libraries, sequencing 100 Gbs of the sequences from those libraries, mapping those sequences against a representative genome, and analyzing what is observed gets close to $100.What is needed now, however, is just a little further push in technology so that we can go from a $2,000 genome to a $100

(or less) genome. That is not going to occur unless there is some competition in the DNA sequencing space. If there is no competition, I fully expect the cost of sequencing per genome to stay almost where it is. If Illumina does have some competition, we will see a much faster push towards the $100 genome and less.

143. If Illumina were to allow BGI to compete with them (or were forced to), the first thing that will happen is that the time to get to the sub $100 30X WGS will be decreased. The recent announcement at the Advances in Genome Biology and Technology Conference in Marco Island, Florida, last month, by Dr. Drmanac of the highest output MGI machine which should be capable of generating 30X WGS for the $100 price point. If BGI is allowed to market these machines outside of China, this would sufficient motivation for Illumina to do further improvements on their platform. This could be either through developing a next generation of high-throughput machines with considerably greater sequence output than the NovaSeq machines, or by reducing their reagent costs. Even in the worst case scenario, let's assume that BGI ended up being responsible for 25% of the 50 million genomes that will be sequenced in the next five years. Illumina would still be in charge of sequencing 75% of those genomes and the competition engendered by Illumina and BGI would more rapidly push the clinical adoption of WGS as (1) something to do for every newborn child, and (2) the assay for analyzing alterations that occur in any cancer. If in this market Illumina were to only have 50% of the market (and I contend that even with BGI being allowed to compete against them, they wouldn't lose that much of this huge market), they would still have a multi-billion dollar business, and again much more rapidly than if they continue to stifle development in the absence of competition.

D. Illumina Will Not Suffer Irreparable Harm in Absence of an Injunction

144. Illumina also discusses how the plans of BGI will greatly hurt them, but even that argument rings false. The Illumina monopoly on high throughput DNA sequencing will also end up costing Illumina profits. While Illumina appears worried that the competition from BGI will mean that less of the 50 million whole genomes sequenced in the next five years will be done on their platform, what they fail to realize is that the faster those 50 million genomes are sequenced and analyzed, the faster we will see the clinical adoption of WGS as a standard clinical assay and for

hundreds of millions of people every single year.

145. It is therefore my opinion that if Illumina were to look at the bigger picture, they too would realize that attempting to muscle out all competition in the sequencing space is actually quite short-sighted and that in the end they would end up hurting themselves more. Instead, by helping to get the various Population-based sequencing projects completed more quickly, they could in the mid- to long-run actually reap even greater profits, even in an environment where they are not the only major sequencing company. By allowing Illumina to maintain their sequencing monopoly, the net effect of this is to increase the amount of time that it will take until the Population sequencing projects are completed, and further delay the time until genomics-driven medicine and true Personalized Medicine becomes a reality.

146. As outlined in the beginning of this declaration, I have been working using molecular biology techniques including DNA sequencing for more than the past three decades. During that period of time I have seen how technological advances in this field have dramatically changed clinical practice. The ability to generate the first draft sequence of the human genome in 2000 was a real game changer as for the first time we had a comprehensive list of the genes present within the human genome. This then led to a large number of clinical assays looking for mutations in important genes involved in different diseases using CE-based Sanger Sequencing.

147. However, all of these advances are absolutely nothing compared to the transformation that will be coming based upon the development and incredible advances that have been made all due to MPS technologies. The reduction of sequencing costs from over 200 million dollars to generate the first draft sequence of the human genome in 2000, to the dawn of the first true sub-$1000 genome just 20 years later has been the most dramatic thing that I have seen in my entire scientific career. It was really exhilarating to watch these technologies develop and improve. It is thus quite unfortunate that once Illumina completely controlled the sequencing space that the era of dramatic improvements on a yearly basis seemed to stop.

148. While the race towards the sub-$1,000 genome has been a technological miracle it is a shame that the lack of competition in the sequencing space appears to have halted further increases in sequencing capabilities. As I outlined above, what is a real shame is that we have come this far, and

then stopped such a short distance from a much more significant finish line, and that is one where the cost of 30X WGS is at the $100, or less, price point. When that point is reached all sequencing-based applications become so easy and affordable that they rapidly herald the true dawn of Personalized Medicine for all. This is why it is so imperative that competition in the sequencing space be encouraged as I have never seen anything in my entire research career that could so completely change clinical practice. It is therefore so important to realize that Illumina's requested injunction against MGI's sequencing products is not at all in the best public interest. Indeed, if the market expands as significantly as I expect it will, it may not even be in the best interest of Illumina itself!

E. BGI's Entrance In the U.S. NGS Market Faces Numerous Hurdles That Will Take Years To Overcome

149. Illumina's claims that, if their patents are not upheld and in absence of an injunction, BGI's sales will immediately and dramatically impact on Illumina's profits, but based on my experience, this is not consistent with the MPS market dynamics.

150. In reality, even if BGI was allowed to start selling their sequencers in the United States, it would take several years for BGI to gain market acceptance and to have an impact on the U.S. MPS market. This is because the adoption of new sequencing platforms by market entrants is a slow, multi-step process. The first step is for KOLs in the field, such as those at large sequencing facilities (like the Broad) or well-known research labs, to start working with the new platforms. These individuals will give the industry comfort in the quality of the data and that the systems are sufficiently robust and durable.

151. Based on my experience, this overall process takes several years, at least. Thus, Illumina's claim that allowing BGI to enter the U.S. market will immediately effect Illumina's overall profitability is, in my opinion, not credible.

152. Moreover, Illumina's claim that allowing BGI to provide their sequencers with StandardMPS reagents to a small number of KOLs will immediately effect their overall profitability is also not credible. Many papers have been published with the StandardMPS chemistry, so it is entirely reasonable for a KOL to want to use the StandardMPS as a comparator to the CoolMPS data output on the DNBSEQ platform. At the first step of this process, KOLs will be interested in exploring the systems' capabilities, but will not be replacing their Illumina (or other) systems with those of BGI. Thus, Illumina faces little risk of harm from BGI in the near-term, but allowing BGI to work with KOLs and to work towards market acceptance for its sequencing products is important for expediting its ability to be a viable competitor after trial, which is in the public's best interest.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on April 10, 2020.

David I Smith, Ph.D.

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PERSONAL DATA: Born May 22, 1954 in Cooperstown, New York.
Married: Denise A. Ducharme
Three children: Matthew 36, Allison 30, Kirstie 29

EDUCATION:

1974	B.S.	University of Wisconsin, Madison Majors: Mathematics and Molecular Biology
1978	Ph.D.	University of Wisconsin, Madison Department of Biochemistry Research Advisor: Dr. Julian Davies Thesis title: "Purification and characterization of aminoglycoside phosphotransferases"

TRAINING:

1978-80	Postdoctoral Student, Albert Einstein College of Medicine, Bronx, New York Advisor: Dr. David Shafritz
1980-82	Senior Research Scientist, Enzo Biochem, New York
1982-85	Postdoctoral Fellow, University of California at Irvine, Advisor: Dr. John Wasmuth

FACULTY APPOINTMENTS:

1985-90	**Assistant Professor**, Department of Molecular Biology and Genetics Wayne State University School of Medicine, Detroit, MI
1986-89	Head, Recombinant DNA Laboratory, a facility of the Center for Molecular Biology
1990-95	Associate Professor, Department of Molecular Biology and Genetics Wayne State University School of Medicine, Detroit, MI
1993-95	**Associate Professor**, Department of Internal Medicine Division of Hematology/Oncology, Wayne State Univ School of Medicine, Detroit, MI
1993-96	Director of the Molecular Oncology Laboratory, Division of Hematology/Oncology Wayne State University School of Medicine, Detroit, MI
1994-96	Director of the Molecular Oncology Program Comprehensive Cancer Center of Metropolitan Detroit (Barbara Ann Karmanos Cancer Inst.)
1995-96	**Professor**, Department of Internal Medicine, Division of Hematology/Oncology Wayne State University School of Medicine, Detroit, MI
1996-	**Professor**, Consultant, Division of Experimental Pathology Director of the Cancer Genetics Program Director of the Gene Identification Laboratory Mayo Clinic Cancer Center Department of Laboratory Medicine and Pathology
1999-2005	Co-Director of the Ovarian Cancer Program of the Mayo Clinic Cancer Center

2009- Chairman, Technology Assessment Group (TAG), Center for Individualized Medicine, Mayo Clinic

MAJOR PROFESSIONAL SOCIETIES:
American Society for the Advancement of Science
American Society for Human Genetics
American Association for Cancer Research
International Papillomavirus Society

HONORS/AWARDS:
National Institutes of Health Senior Postdoctoral Fellowship
Department of Biological Chemistry
University of California at Irvine 1983-85

Basil O'Conner Starter Research Fellowship
March of Dimes Birth Defects Foundation
8/1/87 - 6/30/90

COMMITTEES:

1987-90	Elected to Graduate Council, Wayne State University
1987-89	Scholarship and Fellowship Committee, Graduate Council Wayne State University
1987-90	Faculty Selection Committee, Molecular Biology Genetics, Wayne State University
1985-90	Aerobics Instructor, Wayne State University School of Medicine
1987-89	Basic Science Chairs, Core Curriculum Committee
1987-93	Promotion and Tenure Committee, Department of Molecular Biology
1989-91	Elected to the University Council, Wayne State Univ.
1990-91	Faculty retraining in Molecular Biology Committee
1991-96	Elected to the Academic Senate
1991-96	Research Committee of the Academic Senate
1991-92	Chairman, Molecular Biology and Genetics Seminar Committee
1991-92	Graduate Student Recruitment Committee
1992-93	Co-Graduate Advisor, Cancer Biology Program
1992-96	Executive Committee, Cancer Biology Program
1992-93	Curriculum Committee, Molecular Biology and Genetics
1993-94	DMCIOAD Board of Trustees
1993-96	Research Committee of the Department of Internal Medicine
1994-96	Research Committee of the Division of Hematology/Oncology
1994-96	Member of the Operating Committee of the Comprehensive Cancer Center of Metropolitan Detroit (Barbara Ann Karmanos Cancer Center)
1995-96	Research Committee of the Academic Senate
1995-96	Elected to the Academic Senate (3rd term)
1995-96	Dean's Executive Committee, Wayne State University School of Medicine
1995-96	Research Development Committee of the Academic Senate, WSU
1997-	Director of the Cancer Genetics Program of the Mayo Cancer Center
1997-98	Epidemiology Search Committee, Mayo Foundation
1997-	Director of the Gene Identification Laboratory, Mayo Clinic Cancer Center
1997-98	Tissue Procurement Committee, Mayo Foundation
1998-1999	Director of the Prostate Interactive Working Group, Mayo Foundation
1998	Research Director of the Ovarian Cancer Research Program
1998	Member of the Mayo Clinic Cancer Center Executive Committee
1999-2000	Director Search Committee, Mayo Foundation
1999-2001	Division of Experimental Pathology Search Committee, Mayo Foundation
1999	Research Resource Facilities Subcommittee (RRFS) Chairman, Mayo Foundation, Title changed to Research Technology Subcommittee (RTS) in 2002.
2000-2001	Member of the Genomics Task Force
2001-2003	Member of the Research Executive Committee, Mayo Foundation
2005-2009	Chairman of RCFTS (Research Core Facilities and Technology Subcommittee)

2005-2010 Member of the REES (Research Equipment and Space) Committee
2005-2009 Member of the Genomics Oversight Committee
2006-2009 Member of the Research Oversight Governing Committee (ROCG)
2009- Chairman of the Technology Assessment Group, Center for Individualized Medicine
2013- Member of the Test Development/New Technologies Subcommittee of the Department of Laboratory Medicine and Pathology

STUDY SECTIONS:
1987-95 Comprehensive Cancer Center of Michigan
l989 Mammalian Genetics Study Section, NIH, Special Reviewer
l990-94 Mammalian Genetics Study Section
1992 Howard Hughes Undergraduate Biological Sciences Educ. Initiative External Review panel
1993 National Cancer Institute PO1 Center Review
1994 National Cancer Institute PO1 Centers Review
1994-98 National Institutes of Health, Reviewers Reserve
1995 National Cancer Institute Breast Cancer S.P.O.R.E.'s review committee
1995 National Cancer Institute P50 Centers Review
1996 National Cancer Institute P50 Centers Review
1997 Department of Defense - Breast Cancer review - Genetics section
1998 Department of Defense - Prostate Cancer Review - Genetics section
1998 National Cancer Institute, Breast & Prostate Cancer S.P.O.R.E.'s review committee
1998 National Cancer Institute, U24 Proposals on BAC arrays for the human genome
1998 Department of Defense - Breast Cancer review- Chairman Genetics Section
1998 National Cancer Institute - Review of a PO1 proposal at the Eppley Cancer Center
1999 Department of Defense - Prostate Cancer review- Genetics Section.
1999 National Cancer Institute - Review of the proposals from the Directors Challenge
1999 Department of Defense - Breast Cancer review- Chairman Genetics Section
1999 Department of Defense - Ovarian Cancer review- Chairman OC5, Genetics
2000 National Cancer Institute - Site visit of the Cold Spring Harbor CCSG Grant.
2000 Department of Defense - Concept Award review
2001 Department of Defense - Prostate Cancer review - Chairman Molecular Genetics 1
2001 Department of Defense - Breast Cancer review
2001 American Cancer Society - Molecular Genetics and Oncogenes Study Section - served two terms ad-hoc, then appointed as a regular member (2001-2004)
2001 Department of Defense- Ovarian Cancer review
2001 National Cancer Institute- Review of the Program Project of Dr. Janet Rowley
2001 National Cancer Institute- GI and Prostate SPORE review
2002 National Cancer Institute- Head and Neck SPORE review
2002 National Cancer Institute- Breast cancer SPORE review
2002 Department of Defense- Era of Hope Planning Committee.
2002 Department of Defense- Breast cancer review.
2003 Department of Defense- Prostate and GU cancer review
2003 Department of Defense- Breast Cancer Integration Panel- Ad Hoc
2003 Department of Defense- Breast Cancer Integration Panel- Ad Hoc
2004 National Cancer Institute- Head and Neck SPORE review.
2004 Department of Defense- Breast Cancer Integration Panel- Ad Hoc
2004 Department of Defense- Breast Cancer Integration Panel- Ad Hoc
2005 Department of Defense- Era of Hope Scholars Award- Chairman
2005 National Cancer Institute- Site Visit of Cold Spring Harbor CCSG Grant
2005 National Cancer Institute- Cancer Genetics Study Section- Ad Hoc
2005 New York State Department of Health- Breast Cancer Postdoctoral fellowship review
2006 National Cancer Institute- Pancreatic Cancer SPORE review
2008 Era of Hope (March 20-21) Planning Committee
2008 Era of Hope (June 25-27) Meeting
2009 National Cancer Institute- IRG Subcommittee Career Development grant reviews
2009 Breast Cancer Research Program grant reviews (Sept. 9-10) Council.
2009 NCI ARRA Grand Opportunities Reviews

2009 Department of Defense- Breast Cancer Integration Panel- Ad Hoc
2010 NCI PO1 Study Section Review
2011 NCI Cold Spring Harbor Cancer Center Site Visit
2011 NCI NCA-B review
2011 Era of Hope Planning Committee
2016 Cancer Research UK Review Committee

MEETINGS AND SCIENTIFIC LEADERSHIP

1994 Organized and ran the Fifth International Workshop on Chromosome 3 Mapping, May 8-9, 1994, Ann Arbor, Michigan (with Dr. Thomas W. Glover).
1994 Co-Moderator of Cancer Genetics II Slide Session at the American Society of Human Genetics Meeting in Montreal, Quebec, Oct. 1994.
1995-1997 Head of the Fragile Site Consortium - An NCI-sponsored consortium consisting of the labs of Drs. Harry Drabkin, Robert Gemmill, Michelle LeBeau, Tim McKeithan, & Thomas Glover.
1998 Co-Chairperson of Poster Discussion Session at the American Association for Cancer Research Meeting in New Orleans on Novel Genes and Loci. March 31, 1998.
1998 Organized, obtained funding and ran a National Cancer Institute sponsored Expanded Fragile Site Consortium meeting at the Mayo Clinic on Sept. 18-19, 1998.
1998 Organized and ran a Workshop presented at the American Society of Human Genetics meeting in Denver entitled "Common fragile sites and cancer."
1999 Organized and ran (with C. David James) an International Meeting on Fragile Sites, Gene Amplification and Cancer, Mayo Clinic, August 25-26, 2000.

2014 Chairman of Clinical Genomics, Hansen Wade, Boston MA, Jan. 28-30th, 2014
2014 Chairman of the Companion Diagnostics Meeting, Hansen Wade, Frankfurt, Germany, April 23-24th, 2014
2015 Chairman of RNAseq Europe, Hansen Wade, London, England April 21-23rd, 2015

EDITORIAL BOARDS

2005 Cytogenetics and Genome Research
2014 Journal of Next Generation Sequencing
2015 Front Line Genomics

EDITORIAL REVIEWS

Genomics
Breast Cancer Research
Biochemical Pharmacology
Biotechniques
British Journal of Cancer
Cancer
Cancer Letters
Cancer Research
American Journal of Human Genetics
Gynecologic Oncology
Cytogenetics and Cell Genetics
Clinical Cancer Research
European Journal of Human Genetics
European Journal of Cancer
Gene
Genes, Chromosomes and Cancer
Human Genetics
Human Molecular Genetics
Journal of the National Cancer Institute
Journal of the American Medical Association
Journal of Molecular Diagnosis
Journal of Pathology

International Journal of Cancer
Leukemia
Molecular Carcinogenesis
Molecular and Cellular Biology
Oncogene
Somatic Cell and Molecular Genetics
Trends in Genetics

TEACHING
11 years at Wayne State University

COURSES TAUGHT AT WAYNE STATE:
Molecular Biology and Genetics 770- started and taught 3 times (sole teacher for this 3-credit course)

Cancer Biology 770 - started and taught a Journal Club for the Cancer Biology Program

Molecular Biology and Genetics 701 - guest lecturer

Molecular Biology and Genetics 702 - guest lecturer

Molecular Biology and Genetics Communications Course- guest lectured 2 times

Cancer Biology 720 - Molecular Biology of Cancer Development

Cancer Biology 711 and 712 - Cancer Biology Survey

Developed and taught a course for the Detroit Police Department on DNA fingerprinting - 1991
Medical Genetics - gave one lecture on molecular methodologies, Spring 1994

MLPCCC Core Oncology Lecture/Seminar Series- 1990-1996
I taught four weeks of lectures (each year) to fellows in the Medical Oncology Program

21 years at the Mayo Clinic

COURSES TAUGHT AT MAYO FOUNDATION - Started in early 1997
TBIO 8250 Origins of Human Cancer: Etiology and Genetics, Jan. 14, 1997

Biochemistry and Molecular Biology - 5 lectures on large-scale genomic analysis - Week of Feb. 17 and Feb. 24th, 1997; 4 lectures on large-scale genomic analysis - March 9-16, 1998.

TBIO 8005- Tumor Suppressors- June 10-12, 1997.

Cellular and Molecular Diagnostic Pathology Lecture - Dec. 4, 1997

Genome Analysis- Core Curriculum Course - Dec. 9, 11, 14, 16, 18, 1998

Genome Analysis- Core Curriculum Course - Sept. 27, 29, Oct. 1, 4, 1999

Tumor Biology- Fragile Sites and Cancer - May 8, 2000.

Genome Analysis- Core Curriculum Course - Oct. 18, 20, 23, 2000.

Cancer Genetics- In the Expanded Genetics Core Curriculum - Feb. 6, 10, 2001.

Genome Analysis- Core Curriculum Course- Aug 16, 17, 20, 2001.

Genetics Course- Cancer Genetics, Jan. 30, Feb. 1, 4, 2002.

Genome Analysis- Core Curriculum Course- 2002.

Genetics Course- Cancer Genetics, Feb. 2003.

Genome Analysis- Core Curriculum Course- 4 lectures- August 11-14, 2003.

Genetics Course- Cancer Genetics, Feb. 16, 18, 20th, 2004.

Genome Analysis- Core Curriculum Course- 4 lectures- Aug. 9, 10, 11, 12th, 2004

Genetics Course- Cancer Genetics, Feb. 2, 4, 7th, 2005.

Genome Analysis- Core Curriculum Course- 4 lectures, Aug. 9, 10, 11 and 14th, 2005

Genetics Course- Cancer Genetics

Viral Integration and Cancer

Genome Analysis- Core Curriculum Course- 4 lectures, 2006

Genetics Course- Cancer Genetics- Jan 26, 29 and 31st, 2007

Genome Analysis- Core Curriculum Course- 3 lectures, Aug. 2007

Genetics course- Cancer Genetics- Three lectures, Jan. 2008

Genome Analysis- Core Curriculum Course- 3 Lectures, August 2008

Genome Analysis- Core Curriculum Course- 3 Lectures, August 2009

Genome Analysis Core Curriculum Course- 4 Lectures/year, August 2010- August 2017

Thesis Dissertations Directed at Wayne State University

David Ginzinger - Masters Degree-"Physical mapping & cDNA analysis of a cosmid located in a region of human chromosome 3 associated with small cell lung carcinoma & renal cell carcinoma" - 1991

Nai-dy Wang- Ph.D. degree - "Determination of the specificity of aphidicolin-induced breakage on the human 3p14.2 fragile site" - 1992

Wanguo Liu- Ph.D. degree - "Characterization of DNA sequences surrounding the Von Hippel Lindau disease locus" - 1993

Vasant Jayasankar- Masters Degree - "Characterization of a 3p14 microdissection library: The identification of novel probes in the vicinity of a tumor suppressor locus"- 1993

Scott E. Smith - Ph.D. degree - "Cloning and characterization of the human t(3;6)(p14;p11) translocation breakpoint associated with hematologic malignancies" - 1994

Viji Shridhar - Ph.D. degree - "Cloning and characterization of the region involved in lung cancer on human chromosome 3p" - 1995

William J. Paradee - Ph.D. degree - "Cloning and identifying the human 3p14.2 constitutive fragile site" - 1995

Timothy Drumheller - Ph.D. degree - "Characterization of the chromosome 3 breakpoints in the 3p- syndrome" - 1995

In addition to directing the thesis work of all these students, I was also actively involved in assisting many other graduate students with their Ph.D. projects. Two students that did the vast majority of their Ph.D. work in my laboratory were Asha Kamat (Molecular Biology and Genetics - Ph.D. 1992) and Mark Kaplan (Immunology/Microbiology - Ph.D. 1992)

I was also a member of the thesis committee for 10 students in the Department of Molecular Biology and Genetics and over 20 students in other departments at Wayne State University.

Thesis dissertations directed at Mayo-

Kurt A. Krummel - Biochemistry/Molecular Biology Program- Started Sept. 1996. Completed Sept. 11, 2001. Thesis Title: The characterization of the common fragile site FRA16D and its ortholog in mus musculus.

Erik C. Thorland - Biochemistry/Molecular Biology Program- Started Sept. 1996. Completed November 29, 2001. Thesis Title: HPV integrations preferentially occur in common fragile sites in cervical tumors.

Eric S. Calhoun - Tumor Biology Program- Started Sept. 1997. Completed May 29, 2002. Thesis Title: Molecular characterization of cervix cancer: A gene-based approach to identify transformation related molecular markers.

Gwen Lomberk Callahan - Tumor Biology Program- Started Sept. 1997. Completed Oct. 1, 2002. Thesis Title: Identification of genes involved in the development and/or progression of human serious epithelial ovarian cancer.

Matthew I. Ferber - Biochemistry/Molecular Biology Program- Started Sept. 1998. Completed June 9, 2003. Thesis Title: Non-random integration of human papillomavirus type 18 in cervical carcinomas.

Jessica Silva- Biochemistry/Molecular Biology Program- Started Sept. 2005, Completed March 9, 2011, Thesis Title: Identification and characterization of lncRNAs (long non-coding RNAs) and their association with cancer.

Joseph H. Blommel- Master's Thesis, Thesis Title: Next Generation Sequencing and its role in clinical practice. Completed, 2013.

Terra Lasho- Biochemistry/Molecular Biology Program- Started 2012, Completed: April 18, 2014. Thesis Title: Identification and Characterization of Novel Micro-Alterations and Overt Cytogenetic Breakpoints Using High Resolution Mate-Pair Sequencing in Primary Myelofibrosis

Sarah Kester- Master's Thesis, Thesis Title: Role of Human Papillomavirus in the development of oropharyngeal squamous cell carcinoma. Thesis Defense- October 6, 2014

Course Development

Wayne State University
Molecular Biology and Genetics 770 - Molecular Biology Techniques
Cancer Biology 770 - Seminar Course in Cancer Biology

Mayo Foundation
Core Curriculum Course in Genome Analysis

GRANT SUPPORT:

Research Award Program, WSU
"Using tiny fragments produced by rare-cutting restriction endonucleases to construct precise physical maps of mammalian chromosomes"
Period: 04/01/87-03/31/88, Amount: $6,000

Center for Molecular Biology, WSU
"Construction of a NotI restriction map for human chromosome 3"
Period: 06/01/86-05/31/87, Amount: $10,000

Biomedical Research Support Grant, WSU
"Construction of a physical map for the short arm of human chromosome 3"
Period: 05/01/86-04/30/87, Amount: $11,740

Comprehensive Cancer Center of Michigan
"The isolation of molecular probes near the common fragile site 3p14.2"
Period: 02/02/86-12/31/86, Amount: $7,400

Center for Molecular Biology
"Using cosmids containing clusters of rare restriction sites to construct reproducible maps of mammalian chromosomes"
Period: 08/01/87-07/31/88, Amount: $19,000

March of Dimes Basil O'Connor Starter Research Fellowship
"Distribution of rare restriction sites in human DNA"
Period: 08/01/87- 06/30/90, Amount: $69,840

National Institutes of Health
Co-Investigator. P.I.: O.J. Miller.
"Function of CpG-rich islands in human DNA"
Period: 01/01/88- 07/31/91, Amount: $418,107

Childrens Leukemia Foundation of Michigan
"Isolation and characterization of submicroscopic extrachromosomal elements from human leukemias"
Period: 07/01/88-06/30/90, Amount: $45,025, direct costs.

National Institutes of Health
CA48031 "Characterization of specific chromosome breakpoints associated with renal and small cell lung carcinoma"
Period: 08/01/88- 07/31/91, Amount: $340,000, direct costs

March of Dimes Birth Defects Foundation Basic Research Grant
"Characterization of DNA Sequences surrounding the Von Hippel Lindau Disease Gene"
Period: 07/01/90-06/30/93, Amount: $74,503, direct costs

National Institutes of Health
CA48031 "Characterization of specific chromosome breakpoints associated with renal and small cell lung carcinoma"
Period: 08/01/91-07/31/96, Amount: $875,305, direct costs

Wayne State University
1992-93 Faculty Competition for Graduate Research Assistantships
Period: 09/01/92-08/31/93, Amount: $19,380

Wayne State University
1993-94 Faculty Competition for Graduate Research Assistantships
Period: 09/01/93-08/31/94, Amount: $19,308

National Institutes of Health
"Cancer Center Support Grant" 5 P30 CA22453, Program leader Molecular Genetics (PI William Peters)
Period: 04/01/88-03/31/96, Amount: $1,041,677 for 04/01/95-03/31/96

National Institutes of Health
"Fifth International Chromosome 3 Conference"
Period: 03/01/94-08/31/94, Amount: $16,000, direct costs

Department of Energy
"Fifth International Chromosome 3 Conference"
Period: 03/01/94-08/31/94, Amount: $16,000, direct costs

National Institutes of Health
"MBRS Program at Wayne State University", Associate Investigator (PI Dr. Joseph Dunbar)
Period: 01/01/95-12/31/98, Amount: $4,834,311, My Section $150,000, direct costs.

National Institutes of Health
CA48031 "Chromosome breakpoints and renal and small cell cancer" - Competing Renewal #2
Period: 08/01/96-07/31/01, Amount: $1,482,000, direct costs.

Mayo Foundation, Molecular Medicine Program

"Identification & characterization of molecular defects from individuals with Marfan & related disorders" Period: 05/01/97-04/30/98, Amount: $30,000

Department of Defense
"Genes in FRA16D and FRA7G mutated in prostate cancer"
Period: 10/01/98 - 3/31/01, Amount $312,500 direct costs.

National Institutes of Health, Co-P.I., P.I. Norman Eberhardt
"Tumor Suppressors and Differentiated Thyroid Cancer"
Period: 12/1/98 - 11/30/01, Amount $1,140,781 direct costs.

Department of Defense
Program Project Grant on Ovarian Cancer
"Characterization of genetic alterations in ovarian cancer"
Period: 10/01/99 - 09/30/03, Amount $1,331,330 direct costs.

Minnesota Ovarian Cancer Alliance
“A large common fragile site gene, PARK2, and ovarian cancer.
Period: 6/01/02- 5/31/04, Amount $50,000

Department of Defense
Idea Award Ovarian Cancer Program
“PARK2, a large common fragile site gene, is part of a stress response network in normal cells that is disrupted during development of ovarian cancer”.
Period: 12/15/03 –12/14/06, Amount $547,500

Department of Defense
Breast Cancer Concept Award
Role of highly conserved non-coding RNAs in the development of breast cancer.
Period: 8/1/07- 7/31/08, Amount $75,000

Department of Defense
Breast Cancer Idea Award
Role of a long NNK-induced non-coding transcript in breast cancer
Period: 12/1/09 – 7/31/13, Amount $150,000

Department of Laboratory Medicine and Pathology Collaborative Research Program
Collaborative Award
Developing a liquid biopsy for the monitoring of patients with oropharyngeal squamous cell carcinoma
Period: 12/1/13 – 11/31/15, Amount $275,000

Department of Laboratory Medicine and Pathology Developmental Award
Developing an *in vitro* model for HPV integration
Period: 1/1/18- 12/30/18, Amount $40,000

PUBLICATIONS:

1. **Smith DI**, Gomez-Luz R, Rubio Calvo MC, Datta N, Jacob AE, Hedges RW. Third type of plasmid conferring gentamicin resistance in Pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy* 1975; 8:227-230.
2. **Smith DI**, Blattner FR, Davies JE. The isolation and characterization of a new restriction endonuclease from Providencia stuartii (**PstI**). *Nucl. Acids Res.* 1976; 3:343-353.
3. Hedges RW, Matthew M, **Smith DI**, Cresswell JM, Jacob AE. Properties of a transposon conferring resistance to penicillins and streptomycin. *Gene* 1977; l:241-253.
4. Carlock LC, **Smith DI**, Wasmuth JJ. Genetic counter-selective procedure to isolate interspecific cell hybrids containing single human chromosomes: Construction of cell hybrids and recombinant DNA libraries specific for human chromosomes 3 and 4. *Somat. Cell Mol. Genet*.1986; 12:163-74.
5. **Smith DI**, Golembieski W, Gilbert J, Kizyma L, Miller OJ. Overabundance of rare-cutting restriction endonuclease sites in the human genome. *Nucl. Acids Res*. 1987; 15:1173-1184.
6. **Smith DI**. The isolation of a large number of unique sequence DNA probes that map to 3p14-p23. *Chest* 1987; 91:19S-20S.
7. Seizinger BR, Rouleau GA, Ozelius LJ, Lane AH, Farmer GE, Lamiell JM, Haines J, Yuen JWM, Collins D, Majoor-Krakauer D, Bonner T, Mathew C, Rubenstein A, Halperin J, McConkie-Rosell A, Green JS, Trofatter JA, Ponder BA, Eierman L, Bowmer MI, Schimke R, Oostra B, Aronin N, **Smith DI**, Drabkin H, Waziri MH, Hobbs WJ, Martuza RL, Conneally PM, Hsia YE, Gusella JF. Von Hippel-Lindau disease maps to the region of chromosome 3 associated with renal cell carcinoma. *Nature* 1988; 332:268-269.
8. Gerber MJ, Drabkin HA, Firnhaber C, Miller YE, Scoggin CH, **Smith DI**. Regional location of chromosome 3-specific DNA fragments using a hybrid cell deletion mapping panel. *Amer. J. Human Genet*. 1988; 43:442-451.
9. **Smith DI**, Mangrulker RJ, Geist R, Gilbert J, Kinsman K, Drabkin HA, Golembieski WG. Saturation of human chromosome 3 with unique sequence hybridization probes. *Genomics* 1989; 4:453-459.
10. Drabkin H, Sage C, Green P, Gemmill R, **Smith DI**, Erickson P, Hart I, Ferguson-Smith A, Ruddle F, Tommerup N. Regional and physical mapping studies characterizing the Greig polysyndactyly 3;7 chromosome translocation, t(3;7) (p21.l;p13). *Genomics* 1989; 4:518-529.
11. Drabkin HA, **Smith DI**, Jones C, Jonsen M, Sage M, Gold S, Glover T, Bradley WEC, Gemmill R. Regional and physical mapping studies involving rearrangements of human chromosome 3. 7: Molecular Diagnosis of Human Cancer, Cold Spring Harbor Laboratory, 1989.
12. **Smith DI**, Golembieski W, Drabkin H, Kiousis S. Two cosmids that map to 3p21.l-p21.2 that contain clusters of rare restriction sites and evolutionarily conserved sequences. *Amer. J. Hum. Genet*. 1989; 45:443-447.
13. Baldini A, **Smith DI**, Rocchi M, Miller OJ, Miller DA. A human alphoid DNA clone from the EcoRI dimeric family, genomic and internal organization and chromosomal assignment. *Genomics* 1989; 5:822-828.
14. Kiousis S, Drabkin H, **Smith DI**. Isolation and mapping of a polymorphic DNA sequence on chromosome 3 (D3S94). *Nucl. Acids Res*. 1989; 17:5876.
15. **Smith DI**, Kiousis S, Drabkin H, Wasmuth J. Isolation and mapping of a polymorphic sequence on chromosome 3 (D3S8). *Nucl. Acids Res*. 1989; 17:5877.
16. **Smith DI**, Kiousis S, Miller D, Aleixandre C, Wasmuth J. Isolation and mapping of a polymorphic DNA sequence on chromosome 3 (D3S95). *Nucl. Acids Res*. 1989; 17:5878.
17. Capriglione T, Olmo E, Odierna G, **Smith DI**, Miller OJ. Genome composition and tandemly repetitive sequence at some centromeres in the lizard Podarcis s.sicula. *Genetica* 1989; 79:85-91.
18. Hsieh W-T, Fong D, Sloane BF, Golembieski W, **Smith DI**. Mapping of the gene for human cystein Proteinase inhibitor StefinA, STF1, to chromosome 3cen-q21. *Genomics* 1991; 9:207-209.
19. Seizinger BR, **Smith DI**, Filling-Katz MR, Neumann H, Green JS, Choyke PL, Anderson KM, Freiman RN, Klauck SM, Whaley J, Decker H-JH, Hsia YE, Collins D, Halperin J, Lamiell JM, Oostra B, Waziri MH, Gorin MD, Scherer G, Drabkin HA, Aronin N, Schinzel A, Martuza RL, Gusella JF, Haines JL. Genetic flanking markers refine diagnostic criteria and provide insights into the genetics of Von Hippel Lindau disease. *Proc. Nat. Acad. Sci. USA* 1991; 88:2864-2868.
20. Fong D, **Smith DI**, Hsieh W-T. The human kinenogen gene (KNG) mapped to chromosome 3q26-qter by analysis of somatic cell hybrids using polymerase chain reaction. *Human Genet*. 1991; 87:189-192.

21. Gemmill RM, Garcia M, **Smith DI**, Erickson P, Miller YE, Coyle-Morris J, Tommerup N, Drabkin HA. A 2.5 Mb physical map within 3p21.1 detects the breakpoint associated with Greig Cephalopolysyndactyly Syndrome. *Genomics* 1991; 11:93-102.
22. Golembieski W, Smith SE, Recchia FR, Judge A, Shridhar V, Miller OJ, Drabkin HA, **Smith DI**. Isolation of large numbers of chromosome 3-specific cosmids containing clusters of rare restriction sites. *Amer. J. Hum. Genet*. 1991; 49:581-589.
23. **Smith DI**, Liu W, Ginzinger D, Green P, Smith S, Wang N-D, Recchia F, Carolyn K, Drabkin HA, Golembieski W. Localization of 616 human chromosome 3-specific cosmids using a somatic cell hybrid deletion mapping panel. *Genomics* 1991; 11:179-81.
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26. Wernette C, Saldanha R, **Smith DI**, Ming D, Perlman P, Butow RA. A complex recognition site for the group I intron-encoded endonuclease I-SceII. *Molec. Cell. Biol*. 1992; 12:716-723.
27. Liu W, Vance JD, **Smith DI**. cA479 (D3S719) a cosmid mapped telomeric of the Von Hippel Lindau disease gene contains the D3S18 locus. *Human Molec. Genet*. 1992; 1:201.
28. Wang N-D, Testa JR, **Smith DI**. Localization of 3 novel hybrid breakpoints and 18 cosmids in the human 3p13-p21.1 region. *Genomics* 1992; 14:891-896.
29. Kamat AK, Rocchi M, **Smith DI**, Miller OJ. The lamin A/C gene and a related sequence map to human chromosomes 1q23-q44 and 10q11.2-qter. *Somat. Cell Molec. Genet*. 1993; 19:203-208.
30. Wang N-D, Testa JR, **Smith DI**. Determination of the specificity of aphidicolin-induced breakage of the human 3p14.2 fragile site. *Genomics* 1993; 17:341-347.
31. Pericak-Vance P, Nunes K, Whisenant E, Loeb D, Small K, Stajich J, Rimmler J, Yamaoka L, **Smith DI**, Drabkin H, Vance J. Genetic mapping of dinucleotide repeat polymorphisms and Von Hippel Lindau disease on chromosome 3p25-p26. *J. Med. Genet*. 1993; 30:487-491.
32. Kaplan MH, **Smith DI**, Sundick R. Identification of a G protein coupled receptor induced in activated T cells. *J. Immunol*. 1993; 151:628-636.
33. Liu W, Piechocki M, Lyles G, Song Z, Nakamura Y, Drabkin H, Vance J, **Smith DI**. The isolation of a contig of overlapping yeast artificial chromosome (YAC) clones extending for 2.5 megabases in the vicinity of the Von Hippel Lindau disease gene. *Hum. Molec. Genet*. 1993; 2:1177-1182.
34. Smith SE, Joseph A, Nadeau S, Shridhar V, Gemmill R, Drabkin H, Knuutila S, **Smith DI**. Cloning and characterization of the human t(3;6)(p14;p11) translocation breakpoint associated with hematologic malignancies. *Cancer Genet. Cytogenet*. 1993; 71:15-21, 1993.
35. **Smith DI**, Alonso M. Cloning of tumor suppressor genes involved in solid tumor development. *J. Otolaryngol*. 1993; 119:1210-1216.
36. Loeb D, Liu W, **Smith DI**, Vance JM. Dinucleotide repeat polymorphisms in the VHL region of human chromosome 3p25. *Hum. Molec. Genet*. 1993; 2:1746.
37. Bardenheuer W, Schutte J, Szymanski S, Lux A, Ludecke H-J, Horsthemke B, Claussen U, Senger G, **Smith DI**, Wang N-D, LePaslier D, Cohen D, Heppell-Parton A, Rabbitts P, Opalka B. Characterization of a microdissection library from human chromosomal region 3p14. *Genomics* 1994; 19:291-297.
38. Shridhar V, Siegfried J, Alonso M, **Smith DI**. Genetic instability of microsatellite sequences in many non-small cell lung carcinomas. *Cancer Res*. 1994; 54:2084-2087.
39. Siden T, Kumlien J, Drumheller T, Smith SE, Rohme D, Lehrach H, **Smith DI**. Identification of human 3p14.2-p21.3 region-specific YAC clones using Alu-PCR products from a radiation hybrid. *Somatic Cell Mol. Genet*. 1994; 20:137-142.
40. Siden T, Golembieski W, Kumlien J, Rohme D, **Smith DI**. Physical map of the small cell lung cancer deletion region on the short arm of human chromosome 3 (3p13-p22) based on characterizing chromosome 3p radiation hybrids. *Somatic Cell Molec. Genet*. 1994; 20:121-131.
41. Swaroop A, Yang-Feng T, Liu W, Barrow LL, Chen K-C, Meisler M, **Smith DI**. Molecular characterization of a novel human gene, SEC13R, related to the yeast secretory pathway gene SEC13, and mapping to a conserved linkage group on human chromosome 3p24-p25 and mouse chromosome 6. *Hum. Molec. Genet.* 1994; 3:1281-1286.

42. Decker H-JH, Klauck SM, Lawrence JB, McNeil J, **Smith DI**, Gemmill RM, Sandberg AA, Neumann HHP, Simon B, Green J, Seizinger BR. Cytogenetic and fluorescence in situ hybridization studies on sporadic and hereditary tumors associated with von Hippel-Lindau syndrome (VHL). *Cancer Genet. Cytogenet*. 1994; 77:1-13.
43. Shridhar V, Golembieski W, Kamat A, Smith SE, Phillips N, Miller OJ, Miller Y, **Smith DI**. Isolation of two contigs of overlapping cosmids derived from human chromosomal band 3p21.1 and the identification of 5 new 3p21.1 genes. *Somat. Cell Molec. Genet*. 1994; 20:255-265.
44. **Smith DI**, Glover TW, Gemmill R, Drabkin H, O'Connell P, Naylor SL. Report of the Fifth International Chromosome 3 Workshop. *Cytogenet. Cell Genet*. 1995; 68:125-146.
45. Cotter PD, Drabkin HA, **Smith DI**, Bishop DF. Assignment of the human housekeeping gamma-amino levulinate synthase (ALAS1) gene to the distal region of band 3p21.1 by PCR analysis of somatic cell hybrids. *Cytogenet. Cell Genet*. 1995; 69:207-208.
46. Cid LP, Montrose-Rafizadeh C, **Smith DI**, Guggino WB, Cuttings GR. Cloning of a putative human voltage-gated chloride channel (CIC-2) cDNA and mapping of the gene to chromosome 3q26-qter. *Hum. Molec. Genet*. 1995; 3:407-413.
47. Paradee W, Mullins C, He Z, Glover TW, Wilke C, Opalka B, Schutte J, **Smith DI**. Precise localization of aphidicolin-induced breakpoints on the short arm of human chromosome 3. *Genomics* 1995; 27:108-112.
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50. Wilke CM, Hall BK, Miller D, Hoge A, Paradee W, **Smith DI**, Glover TW. Identification of a spontaneous HPV16 integration site within the FRA3B region: Direct evidence for the coincidence of viral integration sites and fragile sites. *Hum. Molec. Genet*. 1996; 5:187-192.
51. Bardenheuer W, Michaelis S, Lux A, Vieten L, Brocker F, Julcher K, Siebert R, Willers C, van der Hout A, Buys CHCM, **Smith DI**, LePaslier D, Cohen D, Schutte J, Opalka B. Construction of a consistent YAC contig for human chromosome region 3p14.1. *Genome Res*. 1996; 6:176-186.
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54. Paradee W, Wilke CM, Wang. L, Shridhar R, Mullins CM, Hoge A, Glover TW, **Smith DI**. A 350 Kb cosmid contig in 3p14.2 that crosses the t(3;8) hereditary renal cell carcinoma translocation breakpoint and 17 aphidicolin-induced FRA3B breakpoints. *Genomics* 1996; 35:87-93.
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58. Shridhar V, Wang L, Rosati R, Paradee W, Shridhar R, Mullins C, Sakr W, Grignon D, Miller OJ, Sun QC, Petros J, **Smith DI**. Frequent breakpoints in the region surrounding FRA3B in sporadic renal cell carcinomas. *Oncogene* 1997; 14:1269-1277.
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61. Willett CG, **Smith DI**, Shridhar V, Wang MH, Emanuel RL, Patidar K, Graham SA, Zhang F, Hatch T, Sugarbaker DJ, Sunday ME. Differential screening of a human chromosome 3 library identifies hepatocyte growth factor-like/macrophage stimulating protein and its receptor in injured lung: Possible implications for neuroendocrine cell survival. *J. Clin. Invest*. 1997; 99:2979-2991.
62. Luan X, Shi G, Zohouri M, Paradee W, **Smith DI**, Decker HJ, Cannizzaro LA. The FHIT gene is alternatively spliced in normal kidney and renal cell carcinoma. *Oncogene* 1997; 15:79-86.
63. Erdmann J, Shimron-Abarbanell D, Shridhar V, **Smith DI**, Propping P, Nöthen M. Assignment of the human serotonin 1F receptor gene (HTF1F) to the short arm of chromosome 3 (3p13-p14.1). *Molec. Membrane Biol*. 1997, 14: 133-135.
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65. Wang X-Y, **Smith DI**, Frederick L, James CD. Analysis of EGF receptor amplicons reveals amplification of multiple expressed sequences. *Oncogene* 1998; 1:191-195.
66. Huang H, Qian C, Jenkins RB, **Smith DI**. FISH mapping of YAC clones at human chromosomal band 7q31.2: Identification of YACs spanning FRA7G within the common region of LOH in breast and prostate cancers. *Genes Chromosom. Cancer* 1998; 21:152-159.
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68. LeBeau MM, Drabkin H, Glover TW, Gemmill R, Rassool FV, McKeithan TW, **Smith DI**. A FHIT tumor suppressor gene? *Genes Chromosom. Cancer* 1998; 21:281-289.
69. Huang H, Qian J, Proffitt J, Wilber K, Jenkins R, **Smith DI**. FRA7G extends over a broad region: Coincidence of human endogenous retroviral sequences (HER-V) and small polydispersed circular DNAs (spcDNA) and fragile sites. *Oncogene* 1998; 16:2311-2319.
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71. Wang X-Y, Liu W, **Smith DI**, James CD. GBAS, a novel gene encoding a protein with tyrosine phosphorylation sites and a transmembrane domain, is co-amplified with EGFR. *Genomics* 1998; 49(3):448-51.
72. Liu W, **Smith DI**, Thibodeau S, James CD. Denaturing high performance liquid chromatography (DHPLC) used in the detection of germline and somatic mutations. *Nucl. Acids Res*. 1998; 26:1396-1400.
73. LeBeau MM, Rassool FV, Neilly ME, Espinosa III R, Glover TW, **Smith DI**, McKeithan TW. Replication of a common fragile site, FRA3B, occurs late in S phase and is delayed further upon induction: implications for the mechanism of fragile site induction. *Hum. Molec. Genet*. 1998; 7:755-761.
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75. Mai M, Yokomizo A, Tindall DJ, Qian C, Yang P, **Smith DI**, Liu W. Activation of silent alleles of p73 in lung cancer. *Cancer Res*. 1998; 58: 2347-2349.
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212. **Smith DI**, Laborde RR, Wang V, Greenberg A, Tombers N, Eckloff B, Smith T, Olsen E, Moore E, Olsen K. Inactivation of expression of many extremely large genes in oropharyngeal cancer. AGBT 2011, Poster Presented.
213. **Smith DI**, Laborde RR, Wang V, Middha S, Smith T, Olson E, Tombers N, Ma J. Exome, transcriptome and methlyome analysis of oropharyngeal cancer. AGBT 2012, Platform Presentation. 2/16/12
214. **Smith DI**, Laborde RR, Wang V, Ma J, Smith T, Olson E. Exome, transcriptome and methylome analysis of oropharyngeal cancers. ISCO 2012, Palma de Mallorca, Oral Presentation, 3/5/12
215. Wang VW, Laborde RR, Asmann YW, Li Y, Ma J, Eckloff B, Tombers NM, Olsen SM, Moore EJ, Olsen KD, **Smith DI**. Identifying novel chromosome fusions out of RNAseq data from oropharyngeal cancers. AACR Annual Meeting, 2012, Abstract #3100. Poster presentation.
216. **Smith DI**, Laborde RR, Wang V, Ma J, Smith T, Olson E. Exome, transcriptome and methylome analysis of oropharyngeal cancers. ISCO 2012, Mallorca, Spain, 2012.
217. Silva, S, **Smith DI**. Long stress induced non-coding transcripts (LSINCTs) and cancer. Non-coding RNA meeting, Miami, FL, Jan 9-11, 2012.
218. **Smith DI**, Wang V, Laborde R, Tombers N, Moore E, Kasperbauer J, Olsen K. Global inactivation of the largest human genes in oropharyngeal cancer. AGBT 2013.
219. **Smith DI.** The identification of long stress-induced non-coding transcripts. CHI RNAseq Lisbon, Dec 4-6, 2013.

220. **Smith DI.** Multiple large genes targeted by genomic instability in oropharyngeal squamous cell carcinoma. ISABS 2013, Split, Croatia, June 25-28th, 2013.
221. **Smith DI**, Gao G. Next generation sequencing to characterize the genomes and transcriptomes of OPSCC. IFNOS meeting 2014.
222. **Smith DI**, Gao G, Wang V, Tombers N, Kasperbauer J. Decreased expression of multiple large common fragile site genes in oropharyngeal squamous cell carcinoma. IFNOS meeting 2014.
223. Gao G, **Smith DI,** Johnson S, Kasperbauer J, Tombers N, Vasmatzis G. The role of human papillomavirus in the development of cancer. HPV 2014 Abstract, Seattle, WA, August 2014.
224. **Smith DI**, Gao G, Tombers N, Kasperbauer J. Human papillomavirus and the inactivation of expression of multiple large common fragile site genes in oropharyngeal squamous cell carcinoma. AACR abstract, AACR, San Diego, CA.
225. Gao G, **Smith DI**, Johnson S, Kasperbauer J, Tombers N, Vasmatizis G. Role of HPV in the development of OPSCC. IFNOS 2014 Abstract.
226. Walker DL, Highsmith EW, Halling KC, Jen J, Kipp BR, Campion MB, Voss JS, Kottschade LA, Holmes MW, Veldhuizen TL, Couch FJ, **Smith DI**, McWilliams RR, Markovic SN, Wieben ED, Cunningham JM, Liu MC. Assay development for BRAF V600E detection in cell-free (cfDNA) using digital droplet PCR. 2014 Mayo CIM Conference Abstract.
227. Gao G, **Smith DI.** Human papillomavirus and cancer. Advances in Genome Biology and Technology, 2015 Conference Abstract.
228. Gao G, **Smith DI**. MP-Seq is a powerful clinical tool for the management of cancer patients. 6th NGS Meeting, Singapore 2016 Conference Abstract.
229. Gao G, Pauley C, Johnson SH, Vasmatzis G, **Smith DI**. Mate-pair sequencing (MP-Seq) as a powerful clinical tool for cancers with a human papillomavirus (HPV) etiology. Advances in Genome Biology and Technology, 2016 Conference Abstract.
230. **Smith DI**. Mate-pair Sequencing (MP-Seq) as a powerful clinical tool for the characterization of cancers with a human papillomavirus etiology. Biomarkers 2017 Conference.
231. **Smith DI**. Human papillomavirus plays different roles in the development of oropharyngeal squamous cell carcinoma than it does in cervical cancer. Virology 2017 Conference.
232. **Smith DI**, and Gao G. Role of HPV in the development of oropharyngeal squamous cell carcinoma (OPSCC). Annual HPV Conference, Cape Town, South Africa.
233. **Smith DI**, Gao G, DRamanzic R, Kasperbauer J, Zhao Y, Gou H, Wang J. Using different next generation sequencing technologies to study the role of human papillomavirus integration in the development of cancer. ICG-12, BGI Conference in Shenzhen.
234. **Smith DI**. The DNA sequencing revolution and its' impact on clinical oncology. Clinical Oncology 2018 Dublin.
235. **Smith DI**. Using different next generation sequencing technologies to study the role of human papillomavirus integration in the development of cancer. Clinical Oncology 2018 Dublin.
236. **Smith DI**. Whole genome sequencing strategies for the management of patients with oropharyngeal squamous cell carcinoma. International HPV Conference 2018, Sydney.
237. **Smith DI**. Using different next generation sequencing technologies to study the role of human papillomavirus integration in the development of cancer. WCCRB 2018, Toronto.
238. **Smith DI**, Gao G, Wang J. Whole genome sequencing to study the role of HPV integration in oropharyngeal squamous cell carcinoma. AACR 2018 meeting, BGI-sponsored session.
239. **Smith DI**. Whole genome sequencing as a valuable clinical tool for the management of cancer patients. Pharmacogenomics and Genetics Conference 2018 Philadelphia.
240. **Smith DI**, and Gao G. Whole genome sequencing strategies to characterize human papillomaviruses role in the development of cancer. Pharmacogenomics and Genetics Conference 2018 Philadelphia.

PRESENTATIONS:

Construction of a recombinational linkage map for human chromosome 3. Wayne State University, Detroit, MI. April, 1985.

Construction of a physical map for human chromosome 3. Seminar, Henry Ford Hospital, Detroit, MI. March 4, 1986.

The isolation of a large number of unique sequence DNA probes that map to 3p14-p23. Presentation, Aspen Lung Conference, Aspen, CO. April, 1986.

Construction of a physical map for human chromosome 3. Seminar, Wayne State University, Department of Physiology, Detroit, MI. September 9, 1986.

Using cluster of rare restriction endonuclease sites for mapping large human chromosomes. Seminar, Wayne State University, Department of Immunology/Microbiology, Detroit, MI. December 16, 1986.

Isolation of large numbers of chromosome 3p-specific probes. Frederick National Cancer Institute, Frederick, MD. March 5, 1987.

Non-random distribution of rare restriction endonuclease sites in human DNA. National Institutes of Health, Bethesda, MD. March 6, 1987.

Non-random distribution of rare restriction endonuclease sites in human DNA. National Cancer Institute, Bethesda, MD. March 7, 1987.

Using cosmids containing clusters of rare restriction sites to construct reproducible maps of mammalian chromosomes. University of Michigan, Ann Arbor, MI. April 22, 1987.

Constructing physical maps of mammalian chromosomes. Montreal Cancer Institute, Montreal, Canada. June 10, 1987.

Constructing physical maps of mammalian chromosomes. Wayne State University, Department of Biochemistry, Detroit, MI. May 10, 1987.

Progress in the physical dissection of human chromosome 3. American Society for Human Genetics 1987 Annual Meeting, San Diego, CA. October 9, 1987.

Using cosmids containing cluster of rare restriction sites to construct complete physical maps of mammalian chromosomes. Somatic Cell Genetics Conference. Grand Traverse Resort Village, Grand Traverse, MI. January 21, 1988.

Using cosmids containing cluster of rare restriction sites to construct complete physical maps of mammalian chromosomes. The Medical College of Toledo Distinquished Lecture Series, Toledo, OH. March 29, 1988.

Molecular characterizations of the constitutive fragile site mapping to 3p14.2. Harper Hospital, Detroit, MI. November 7, 1988.

Molecular Approaches to the Human Genome Initiative. Annual Conference of the Michigan Community College Biologists. Livonia, MI. April 8, 1989.

Construction of a Gene Map For Human Chromosome 3 and Corresponding Mouse Map. Eleanor Roosevelt Institute, Denver, CO. May 11, 1989.

Using cosmids containing clusters of rare restriction sites to identify new genes. March of Dimes 1989 Michigan Symposium, Tools for DNA Analysis. VA Medical Center, Harper Hospital, Detroit, MI. Sept. 28, 1989.

Mapping large regions of mammalian DNA. Southwestern Medical Center, Dallas, TX. Oct. 10, 1989.

Cloning the genes for small cell lung carcinoma, renal cell carcinoma, and Von Hippel Lindau Disease. V.A. Hospital, Bethesda, MD. November 15, 1989.

Saturation of human chromosome 3 with cloned localized probes and the identification of chromosome 3-specific genes. First International Chromosome 3 Conference, San Antonio, TX. February 16, 1990.

Cloning the gene for Von Hippel Lindau disease. Massachussetts General Hospital, Boston, MA. May 8, 1990.

Identifying the gene(s) responsible for the development of renal and small cell lung carcinoma. Wayne State University Department of Chemistry, Detroit, MI. January 18, 1991.

The role of the human genome initiative will play in preventing human disease. Midyear Midwest Conf. of the American Osteopathic College of Preventative Medicine, Dearborn, MI. March 14, 1991.

Saturation of human chromosome 3 with cloned probes. Second International Chromosome 3 Conference, Denver, CO. April 4, 1991.

Identification of genes from human chromosomal band 3p21. Second International Chromosome 3 Conference, Denver, CO. April 5, 1991.

Characterization of chromosomal band 3p21 in search of tumor suppressor genes that play a role in lung cancer & renal cell carcinoma. 3rd International Chromosome 3 Conference, Tokyo, Japan. Mar. 15, 1992.

Cloning the 3p14.2 constitutive fragile site. The Lung Program of Harper Hospital, Detroit, MI. April 16, 1992.

Progress in the cloning of the Von Hippel Lindau Disease gene. The Lung Program of Harper Hospital, Detroit, MI. September 15, 1992.

Cloning of a 3p21 tumor suppressor. The Lung Program of Harper Hospital, Detroit, MI. Dec. 17, 1992.

Progress in the cloning of the Von Hippel Lindau Disease gene. The Cleveland Clinic Foundation, Cleveland, OH. January 8, 1993.

Progress in the cloning of the Von Hippel Lindau disease gene. Bristol-Myers Squibb, Princeton, NJ. January 26, 1993.

Isolation of the region surrounding the Von Hippel Lindau disease gene in a contig of overlapping yeast artificial chromosome clones. Department of Pharmacology, Detroit, MI. January 29, 1993.

Isolation of the region surrounding the Von Hippel Lindau disease gene in a contig of overlapping yeast artificial chromosome clones. Boston University School of Medicine, Boston, MA. February 1, 1993.

Molecular definition of the constitutive 3p14.2 fragile site. Wayne State University, Department of Molecular Biology and Genetics, Detroit, MI. February 8, 1993.

PCR: A powerful technique and some applications. Wayne State University, Grand Rounds, Hematology/Oncology, Detroit, MI. March 1, 1993.

Progress in the cloning of the genes for Von Hippel Lindau disease and renal cell carcinoma. Urologic Oncology Seminar Series, Detroit, MI. March 3, 1993.

Isolation of the region surrounding the Von Hippel Lindau disease gene in overlapping yeast artificial chromosomes. Milton S. Hershey School of Medical Sciences, Hershey, PA. March 22, 1993.

Isolation of the region surrounding the Von Hippel Lindau disease gene in overlapping yeast artificial chromosomes. University of Connecticut School of Medicine, Farmington, CT. April 6, 1993.

Isolation of the region surrounding the Von Hippel Lindau disease gene in overlapping yeast artificial chromosomes. Department of Human Genetics, University of Michigan, Ann Arbor, MI. April 7, 1993.

Cloning of the human 3p14.2 constitutive fragile site. Free University, Amsterdam, Netherlands. May 19, 1993.

Cloning of the human 3p14.2 constitutive fragile site. The Milton S. Hershey School of Medical Sciences, Hershey, PA. May 26, 1993.

Tumor suppressor genes on the short arm of human chromosome 3 involved in lung tumor progression: A difficult target. The Lung Cancer Symposium at Harper Hospital, Detroit, MI. June 17, 1993.

Progress in the cloning of the genes involved in solid tumor development. St. Johns Hospital, Detroit, MI. July 29, 1993.

Positional cloning for the identification of chromosome 3-specific genes that play a role in solid tumor development. The Fourth Annual Cancer Research Conference, ACS Michigan Chapter, Ann Arbor, MI. September 10, 1993.

The Human Genome Initiative: Molecular tools utilized for the characterization and mapping of complex genomes. Department of Chemistry, Wayne State University, Detroit, MI. September 20, 1993.

The molecular cloning of the t(3;6)(p14.2;p11) chromosomal translocation associated with hematologic malignancies identifies several genes in the vicinity of the breakpoint. American Society of Human Genetics meeting. October 8, 1993.

Snakes: Their biology and genetics. Presented to two classes of students at Cody High School, Detroit, MI. October 25, 1993.

Cloning of chromosome 3 genes involved in solid tumor development. Grand Rounds, Hematology/ Oncology, Wayne State University School of Medicine, Detroit, MI. November 5, 1993.

Microsatellite Instability in Lung Cancer. The Lung Program at Harper Hospital, Detroit, MI. February 17, 1994.

The Worldwide Project to Map and Sequence the Human Genome. Plenary Speaker at the Junior Science and Humanities Symposium, McGregor Conference Center, Detroit, MI. March 4, 1994.

The cloning of tumor suppressor genes for the short arm of human chromosome 3. Plenary Speaker at the Third International Symposium on the Biology of Renal Cell Carcinoma. Ritz-Carlton, Cleveland, OH. March 7, 1994.

Molecular characterization of the 3p14.2 constitutive fragile site. Departments of Microbiology, and Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN. March 21, 1994.

The Biological and Genetic Basis of Cancer. Brazilian Cancer Society on their visit to the Detroit Medical Center. Harper Hospital, 2 Weber Center Classroom. May 24, 1994.

Molecular Alterations in Cancer. Division of Hematology/Oncology Grand Rounds, Wayne State University School of Medicine, Detroit, MI. September 21, 1994.

Identification of a highly conserved arginine-rich gene (MRC) from human chromosomal band 3p21.1 that contains point mutations in many renal cell carcinomas. Winship Cancer Center at Emory University, Atlanta, GA. October 15, 1994.

Identification of a highly conserved arginine-rich gene (MRC) from human chromosomal band 3p21.1 that contains point mutations in many renal cell carcinomas. American Society of Human Genetics meeting, Montreal, Quebec. October 21, 1994.

Molecular cloning of FRA3B. Center for Molecular Medicine, Emory University School of Medicine, Atlanta, GA. January 30, 1995.

Current and future applications of molecular biology to cancer treatment. Department of Internal Medicine Grand Rounds, Wayne State University School of Medicine. March 8, 1995.

Molecular cloning of FRA3B. Department of Pharmacology, Wayne State University School of Medicine. March 31, 1995.

Isolation of a new gene mutated in solid tumors. Division of Hematology/Oncology Grand Rounds, Wayne State University School of Medicine. April 26, 1995.

Molecular cloning of FRA3B. Lung Program at Harper Hospital. May 11, 1995.

Isolation of a new gene containing an imperfect trinucleotide repeat mutated in breast cancers. Cancer Program of the Barbara Ann Karmanos Cancer Center. September 6, 1995.

Mutations in a novel chromosome 3 gene (ARP) in many different solid tumors. St. Johns Hospital, Detroit, MI. November 7, 1995.

Mutations in pancreatic cancer: New molecular markers. Pancreatic Cancer Research Program of Harper Hospital. January 9, 1996.

Mutations in ARP in prostate cancer and renal cell carcinoma. GU Oncology Program, Harper Professional Building. January 10, 1996.

FRA3B: Molecular structure and its role in chromosome breakpoints in solid tumors. Pancreatic Program at Wayne State University. February 12, 1996.

FRA3B and breakpoints in cancer. Mayo Clinic, Rochester, MN. March 7, 1996.

FRA3B breakpoints and cancer. Louisiana State University Medical Center. March 15, 1996.

FRA3B breakpoints in cancer. University of Chicago Medical School. March 22, 1996.

Mutations in genes with cryptic repeats in cancer. AACR meeting in Washington, D.C. April 24, 1996.

FRA3B and breakpoints in pancreatic cancer. Pancreatic Program, Wayne State University. April 31, 1996.

New molecular markers for renal cell carcinoma. Renal Cell Carcinoma Conference in Virginia. September 19, 1996.

FRA3B breakpoints in pancreatic cancer. Pancreatic Cancer Research Program. October 11, 1996.

Molecular structure of the most active common fragile site FRA3B: Its role in chromosomal breakage in solid tumors. Molecular Medicine Seminar Series, University of Texas Health Science Center, San Antonio. November 12, 1996.

Human chromosome 3 and cancer. Mayo Cancer Center Works in Progress. February 21, 1997.

Chromosomal fragile sites and cancer. NCCTG bi-annual meeting. March 6, 1997.

Molecular Genetics of Pancreatic Cancer. G.I. Group, Mayo Foundation. April 1, 1997.

New molecular markers for prostate cancer. Prostate Cancer Interest Group, Mayo Foundation. July 7, 1997.

Common fragile sites and Cancer. Genetics Society Meeting, Mayo Foundation. September 18, 1997.

Common fragile sites and cancer. University of Pittsburgh Cancer Center. December 5, 1997.

Fragile Sites and Cancer. Laboratory Medicine and Pathology Residents. January 21, 1998.

Common fragile sites and prostate cancer. Prostate Interactive Working Group first meeting. Feb. 13, 1998.

Common fragile sites and Cancer. Presentation to Dr. Vanda Lennon's group. March 4, 1998.

New Technologies in Cancer Genetics. Laboratory Society, Foundation House, Mayo Foundation. April 10, 1998.

Common fragile sites and cancer. University of Istanbul. June 16, 1998

The Mayo Clinic Cancer Center Cancer Genetics Program. University of Istanbul. June 16, 1998.

The Mayo Clinic Cancer Center Cancer Genetics Program. Ankara Numune Hospital. June 18, 1998.

Common fragile sites and cancer. Roswell Park Cancer Institute. July 20, 1998.

Common fragile sites and cancer. Mayo Foundation Summer Students Program. July 22, 1998.

Cloning of other common fragile sites. Expanded Fragile Site Consortium Meeting. Sept. 18, 1998.

Molecular genetics of prostate cancer. Urogenesys in Santa Monica, California. October 12, 1998.

Fragile sites and cancer. University of Indiana. October 14, 1998.

Workshop on common fragile sites and cancer. American Society of Human Genetics meeting, Denver, CO. October 28, 1998.

Allele-specific late replication and fragility in the FRA3B region. American Society of Human Genetics meeting, Denver, CO. October 30, 1998.

Common fragile sites and cancer. Bilkent University in Ankara, Turkey. November 9, 1998.

Molecular genetics of prostate cancer. Bilkent University in Ankara, Turkey. November 11, 1998.

Common fragile sites and endocrine tumors. GATA, Ankara, Turkey. November 12, 1998.

Common fragile sites and GI cancer. GI Oncology Group at Mayo Clinic. November 16, 1998.

The role of the common fragile sites in cancer. Albert Einstein College of Medicine to the Department of Molecular Pharmacology. May 17, 1999.

Common fragile sites and cancer. Frontiers in Clinical Genetics at George Washington University. Sept. 16, 1999.

The Human Genome Project and how it will change all of biology. Honors Class: [Genetics in the New Millennium] at Rochester Community and Technical College. Sept. 28, 1999.

Role of the Common Fragile Sites in Cancer Development. Miami Winter Symposium on DNA, RNA and Cancer. February 6, 2000.

The Ovarian Cancer Research Program of the Mayo Clinic Cancer Center. Virginia Medical College, Richmond, VA. March 6, 2000.

The Genetics of Ovarian Cancer in the Post-Genomics Era. Distinguished Lecturer for the Women's Cancer Program at M.D. Anderson Cancer Center, Houston, TX. June 7, 2000.

Transcriptional Profiling to Understand the Underlying Biology of the Development of Ovarian Cancer. Distinguished Lecturer for the Women's Cancer Program at M.D. Anderson Cancer Center, Houston, TX. June 7, 2000.

Transcriptional Profiling to Understand the Underlying Biology of the Development of Ovarian Cancer. Henry Ford Hospital, Detroit, MI. July 14, 2000.

Common Fragile Sites and Cancer. Common Fragile Sites, Gene Amplification and Cancer Meeting, Held at Mayo Foundation. August 25-26, 2000.

Common Fragile Sites and Cancer. University of Nebraska in Omaha. Sept. 11, 2000.

Common fragile sites and the development of cancer. Presented to graduate students at Mayo. September 27, 2000.

Star Trek is here today: Impact of the human genome project on biology. Women's Cancer Program, Mayo Foundation. October 6, 2000.

Impact of the Human Genome Project on Biology. Sigma Chi lecturer, Mayo Foundation. October 17, 2000.

Star Trek is here today: Impact of the human genome project on biology. Eagle's Award Dinner, Rochester, MN. October 23, 2000.

The human genome project and its impact on biology. Clinical Coordinators Conference, Mayo Foundation. October 24, 2000.

HPV integration in common fragile sites and the development of cervical cancer. Gyn/Onc Grand Rounds, Mayo Foundation. November 1, 2000.

Transcriptional Profiling of Ovarian Tumors. Eli Lilly, Indianapolis, IN. November 13, 2000.

Transcriptional Profiling of Ovarian Tumors. Department of Defense Annual Meeting on Ovarian Cancer, Dulles Hilton, Maryland. November 30, 2000.

Generation of a Molecular Profile for Ovarian Cancer. Huntsman Cancer Center, Salt Lake City, Utah. December 15, 2000.

Common Fragile Sites and Cancer. Case Western Reserve, Cleveland, OH. January 19, 2001.

Celebration of Research Keynote Address: Impact of the human genome project on biology. Mayo Foundation, Rochester, MN. January 31, 2001.

The Ovarian Cancer Program of the Mayo Clinic Cancer Center. University of Minnesota. April 13, 2001.

Impact of the Human Genome Project on Biology. NCCTG Annual Meeting, Mayo Foundation. April 25, 2001.

Common fragile sites and Cancer. Department of Microbiology and Molecular Genetics, SUNY Stonybrook, NY. Nov. 19, 2001.

Large common fragile site genes are mutational targets in ovarian cancer. Fox Chase Cancer Center, Philadelphia, PA. April 16, 2002.

Large common fragile site genes are mutational targets in ovarian cancer. University of Michigan Cancer Center, Ann Arbor, MI, April 19, 2002.

Star Trek is here today: Implications of the Human Genome Project. Mayo Foundation Nursing staff. April 15 and 22nd, 2002.

Implications of the Human Genome Project. NCI-CPEN Workshop. June 14, 2002.

Using expression profiling to study the biology of ovarian cancer. Shaw College of the Chinese University of Hong Kong. September 27, 2002.

Viral integration and the development of cervical cancer. Cambridge University, March 24, 2003.

Common fragile site genes: a stress response network within cells? Helene Harris Memorial Trust (HHMT) bi-annual meeting in Stratford Upon Avon. March 25, 2003.

Viral Integration and the development of cancer. Presented at the University of Pittsburgh. April 11, 2003.

Parkin, a large common fragile site gene, involved in cancer development. Johns Hopkins University to the laboratory of Dr. Ted Dawson August 18, 2003.

Large common fragile site genes and cancer. Guthrie Research Institute in Sayre, PA. October 17, 2003.

Highly conserved large genes, common fragile sites, neural development and cancer. Moffitt Cancer Center, Tampa, FL. Feb. 25, 2004.

Common fragile sites, extremely large genes, neural development and cancer. Ovarian Cancer Program SPORE meeting at M.D. Anderson Cancer Center, Houston, TX. March12, 2004.

The Human Genome Project and its impact on Biology. Parrish Medical Center, Titusville, FL. April 15, 2004.

Gene expression profiling of ovarian and cervical cancers: making sense of microarrays. Chinese University of Hong Kong. Oct. 14, 2004.

Common fragile sites, extremely large genes and neurological development. Chinese University of Hong Kong. Oct. 15, 2004.

Breast cancer and the human genome project. Mayo affiliate in Seymour, IN, at a meeting on Breast Cancer. Oct. 30, 2004.

Extremely large common fragile site genes, neurological development and cancer. Heidelberg Fragilomics meeting. Feb. 18, 2005.

My experiences with DNA microarrays for expression profiling. Mayo Microarray Interest Group. April 13, 2005.

Impact of the Human Genome Project on Biology and Medicine. Elderhostel group at the Kahler Hotel. April 22, 2005.

The Human Genome Project and its impact on biology. Valley Hospital (MML presentation) in Ridgewood, NJ. April 26th, 2005.

The Human Genome Project and its impact on biology. North Memorial Hospital, Robbinsdale, MN. May 10th, 2005.

The Human Genome Project and its impact on biology. Elderhostel group meeting at the Kahler Hotel. June 30th, 2005.

Cancer Genetics and the Human Genome Project. Fourth European-American School in Forensic Genetics and Mayo Clinic Course in Advanced Molecular and Cellular Medicine. Dubrovnik, Croatia. Sept. 6, 2005.

Transcriptional profiling. Fourth European-American School in Forensic Genetics and Mayo Clinic Course in Advanced Molecular and Cellular Medicine. Dubrovnik, Croatia. Sept. 6, 2005

Positional cloning to identify cancer-related genes. Fourth European-American School in Forensic Genetics and Mayo Clinic Course in Advanced Molecular and Cellular Medicine. Dubrovnik, Croatia. Sept. 6, 2005.

Impact of the Human Genome Project on our understanding of cancer. Elderhostel Group at the Kahler Hotel. Oct. 10, 2005

Impact of the human genome project on our understanding of cancer. Mid-Michigan Medical Center, Midland, MI. October 18, 2005.

The human genome project and its impact on biology. Genomics Course offered by Mayo. October 19, 2005.

Impact of the human genome project on our understanding of cancer. Elderhostel group at the Heintz Center, RCTC, Rochester, MN. October 27, 2005.

New technologies that will change the way that we practice medicine. Century High School, Rochester, MN. Feb. 17, 2006.

To understand how genomics and genome sequences are changing medical care and practice. Fairview Ridges Hospital, Burnsville, MN. Feb. 24, 2006.

Impact of the human genome project on our understanding of cancer. Valley Baptist in Harlingen, TX. April 11, 2006.

Impact of the Human Genome Project on our understanding of prostate cancer. Prostate Cancer Support Group at the Mayo Clinic. May 10, 2006.

Advances in Cancer Genetics from the Human Genome Project. Cancer Education Program at the Mayo Clinic. May 11, 2006.

Impact of the human genome project on our understanding of cancer. Presbyterian Hospital in Greenville, TX. June 15, 2006.

Impact of the human genome project on our understanding of cancer. St. Joseph Healthcare, Bangor, Maine. June 26, 2006.

Impact of the human genome project on our understanding of cancer. Elderhostel Group at the Kahler Centennial Room, Rochester, MN. June 29, 2006.

Impact of the human genome project on our understanding of cancer. Elderhostel group meeting at Kahler Centennial Room, Rochester, MN. July 25, 2006.

Human Genome 101. Clements ACS Golf Classic, Rochester, MN. August 7, 2006.

Impact of the human genome project on our understanding of cancer. Intermountain State Seminar (IMSS) Jackson Hole, WY. Sept. 22, 2006.

Cancer: A complex genetic disease. Intermountain State Seminar (IMSS) Jackson Hole, WY, Sept. 22, 2006.

Transcriptional profiling using microarrays. Intermountain State Seminar (IMSS) Jackson Hole, WY. Sept. 22, 2006.

Positional cloning to identify important cancer genes. Intermountain State Seminar (IMSS) Jackson Hole, WY. Sept. 22, 2006.

Using the tools provided by the human genome project to better understand endometrial cancer. Parrish Medical Center, Titusville, FL. Oct. 3, 2006.

Impact of the human genome project on our understanding of cancer. Elderhostel Group meeting, Kahler Centennial Room, Rochester, MN. Oct. 5, 2006.

Genomic mapping reveals large abundantly expressed, highly conserved non-coding transcripts which are aberrantly expressed in cancer. City of Hope, Duarte, CA. Jan. 5, 2007.

Non-coding transcripts and cancer development. Applied Biosystems (ABI), Foster City, CA. Feb. 2, 2007.

Genomics and cancer. Mayo's ENT Department. Feb. 19, 2007.

Role of large common fragile site genes in cancer and neurological development. National Cancer Institute, Washington, DC. Mar 23, 2007.

MML: Genomics and its impact on medicine. American Society for Clinical Laboratory Science, Wisconsin State Convention. Madison, WI. April 19, 2007.

Long, highly conserved non-coding transcripts. Actigenics, Toulouse, France. May 11, 2007.

MML: Genomics and its impact on medicine. MML Regional Laboratory Alliance/Physician's Reference Laboratory faculty visit. Overland Park, KS. May 15, 2007.

Impact of the human genome project on our understanding of cancer. Elderhostel group at the Kahler Hotel, Centennial Room. May 23, 2007.

New genomic technologies that will change the way we practice medicine. NCCTG Patient Advocate Symposium. June 12, 2007.

MML: Genomics and its impact on medicine. Missouri Baptist Medical Center, St. Louis, MO. June 21, 2007.

Impact of the human genome project on our understanding of cancer. Elderhostel Group at the Kahler Hotel, Centennial Room. June 28, 2007.

Plenary Lecture: Revolutions in DNA sequencing that will change the way we practice medicine. Biannual Forensics Meeting in Split, Croatia. Sept. 3, 2007.

Non-coding RNAs and their roles in cancer. Biannual Forensics Meeting in Split, Croatia. Sept. 6, 2007.

Positional cloning to identify important genes involved in cancer development. Biannual Forensics Meeting in Split, Croatia. Sept. 6, 2007.

MML: New technologies that will change the way we practice medicine. Riverside Methodist Hospital, Columbus, OH. Sept. 18, 2007.

MML: New technologies that will change the way we practice medicine. MML Community Hospital, Grand Junction, CO. Nov. 9, 2007.

Visiting professorship. New genomic technologies and their impact on research and medicine. Texas Tech. Lubbock, TX. Jan. 16, 2008.

New technologies that will change the way we practice medicine. MML Frontline Laboratory Network. Estes Park, CO. Jan. 23, 2008.

Visiting professorship. Revolutions in DNA sequencing and how they can be used to study alterations in cancer. Chinese Univ of Hong Kong. Feb. 14, 2008.

Revolutions in DNA sequencing and its impact on the study of cancer. NCCTG Patient Advocate Symposium, Mayo Clinic Rochester. June 10, 2008.

Revolutions in DNA sequencing and its impact on cytogenetics. Association of Genetic Technologists invited speaker. Houston, TX. June 13, 2008.

Possible viral etiology in oral tongue cancers from patients without a drinking or smoking history. 7th International Conference on Head & Neck Cancer. San Francisco, CA. Platform presentation. July 20, 2008.

High throughput strategies for the study of head and neck cancers. 7th International Conference on Head & Neck Cancer. San Francisco, CA. Platform presentation. July 21, 2008

MML: Genomics and its impact on medicine. Western Health Care Alliance. Grand Junction, CO. Aug. 14, 2008.

MML: High throughput strategies and its impact on the study of medicine. Montrose Memorial Hospital, Montrose, CO. Aug. 15, 2008.

Developing the Infrastructure for Next Generation DNA sequencing at the Mayo Clinic. Presented at the Washington University Genome Sequencing Center, St. Louis, MO. Sept. 12, 2008.

2009

Direct clinical applications of NextGen DNA sequencing at Mayo Clinic. Presented at 6th ISABS Conference on Human Genome Project Based Application in Forensic Science, Anthropology and Individualized Medicine. Split, Croatia. June 1-5, 2009.

2010

High throughput technologies and their impact on the study of cancer. Jackson University, Jackson, MS. Jan. 8, 2010.

Using massively parallel DNA sequencing to study cancers of the head and neck. .University of Illinois, Urbana/Champaign. Jan. 26, 2010.

New technologies in DNA sequencing that will bring us closer to being able to compete for the X Prize. .Archos X Prize meeting held at the University of Illinois, Urbana/Champaign. Feb. 2, 2010.

High throughput strategies and their impact on the study of medicine. MML-Methodist Hospital Southlake Campus, Gary, IN. April 21, 2010.

Advances in DNA sequencing technologies and their impact on research. Sao Paulo, Brazil. April 28, 2010.

Using massively parallel DNA sequencing to study molecular alterations during the development of oral cancer. Sao Paulo, Brazil. April 30, 2010.

High throughput technologies and their impact on the study of medicine. Lake Health Presentation, Painesville, Ohio. May 14, 2010.

Next generation sequencing reveals changes in allele-specific expression associated with changes in copy number in oral cancers. Human Genome Organization meeting, Montpellier, France. May 21, 2010.

Using massively parallel DNA sequencing to study oral cancers. International Federation of Head and Neck Oral Surgeons, Seoul, Korea. June 16, 2010.

New technologies in DNA sequencing that will transform how we study cancer. Mie University, Mie, Japan. June 21, 2010.

Advances in DNA sequencing technologies and their applications at the Mayo Clinic. University of Tokyo, Tokyo, Japan. June 23, 2010.

Advances in DNA sequencing technologies heralds the dawn of the age of Individualized Medicine. NCCTG Patients Advocates Symposium, Rochester, MN. July 13, 2010.

Using massively parallel DNA sequencing to study cancers of the head and neck. Genomics Interest Group, Mayo Clinic. July 21, 2010.

Impact of recent advances in massively parallel DNA sequencing on clinical practice. Agilent Users meeting, Chicago, IL. August 5, 2010.

Using massively parallel DNA sequencing to study the molecular alterations that occur during the development of oropharyngeal cancer. Midwest Illumina Users Meeting, St. Louis, MO. Aug. 1, 2010.

Next generation sequencing reveals changes in allele-specific expression associated with changes in copy number in oral cancers. CHI Conference on Next Generation Sequencing. Providence, RI. Sept. 28, 2010.

Advances in DNA sequencing technologies heralds the dawn of the age of Individualized Medicine. American Cancer Society in Denver, CO. Oct. 6, 2010.

Advances in DNA sequencing technologies heralds the dawn of the age of Individualized Medicine. American Cancer Society in Colorado Springs, CO. Oct. 7, 2010.

Using massively parallel DNA sequencing to study cancers of the head and neck. Northwestern University, Chicago, IL. Oct. 20, 2010.

Using massively parallel DNA sequencing to study cancers of the head and neck. Sequencing at the Tipping Point, Life Technologies Meeting, San Diego, CA. Dec. 1, 2010.

Advances in DNA sequencing technologies heralds the dawn of the age of Individualized Medicine. Associate Appointment Luncheon, Mayo Foundation House, Rochester, MN. Dec. 9, 2010.

Using massively parallel DNA sequencing to study cancers of the head and neck. University of California, San Francisco, Life Technology Presentation, San Francisco, CA. Dec. 10, 2010.

2011

Advances in DNA sequencing technologies and the impact that this will have in clinical practice. Fort Stockton, Texas, Jan. 26, 2011.

The DNA sequencing revolution. Keynote Speaker at the Celebration of Research (held every other year for 300 high school students to see Mayo in action and learn about career opportunities), Feb. 1, 2011.

Next Generation Sequencing and Mayo. CTSA Grand Rounds, Mayo Clinic, February 25, 2011.

Next Generation sequencing of head and neck cancers. Natal, Brazil, Life Sciences Meeting, March 12, 2011.

The DNA sequencing revolution. Minnesota State Science Fair, Keynote Speaker, March 19, 2011.

RNAseq as a clinical tool. IAOO 2011 Congress, Singapore, July 15, 2011.

Next generation sequencing of head and neck cancers. Singapore Genome Institute, July 18, 2011.

The DNA sequencing revolution. ISABS Congress, Bol, Isle of Brac, July 24, 2011.

Next generation sequencing of cancers of the head and neck. ISABS Congress, Bol, Isle of Brac, July 21, 2011.

Long non-coding RNA and breast cancer. Era of Hope Breast Cancer meeting, Orlando, Florida, August 4, 2011.

2012
Exome, transcriptome and methylome analysis of oropharyngeal squamous cell carcinoma. Advances in Genome Biology and Technology, Marco Island, Florida, Feb. 17, 2012.

Exome, transcriptome and methylome of oropharyngeal squamous cell carcinoma. Molecular Genetics Meeting, Palma de Mallorca, Spain, March 5, 2012.

Using next generation sequencing to analyze the transcriptional output of cells. ABRF 2012 Meeting, Orlando, Florida, March 17, 2012.

Using next generation sequencing to study the transcriptome, exome and methylome of oropharyngeal squamous cell carcinoma. ABRF 2012 Meeting, Orlando, Florida, March 17, 2012.

New technologies that will change how we practice medicine. MML-sponsored talk, Anchorage, Alaska, March 28, 2012.

New technologies that will change how we practice medicine. MML-sponsored talk, Wayland, Wyoming, April 5, 2012.

Using next generation sequencing to study oropharyngeal squamous cell carcinoma. Illumina DNA sequencing summit. Dana Point, California, April 16, 2012.

DNA sequencing revolution. Molecular Pathology Lecture, June 20, 2012.

Using next generation sequencing to better understand oropharyngeal squamous cell carcinoma. University of Groningen, Netherlands, October 4, 2012.

2013
Next generation sequencing of oropharyngeal squamous cell carcinoma. University of Chicago, IL, March 11, 2013.

RNAseq on oropharyngeal squamous cell carcinomas. XGen Congress, San Diego, CA, March 19, 2013.

Next generation sequencing to better understand cancers of the head and neck. ISABS Meeting, Split, Croatia, June 26, 2013.

The DNA sequencing revolution and the enormous amount of data that it will generate. Life Sciences Conference, Eden Prairie, MN, October 11, 2013.

Mate-pair sequencing reveals that HPV integration is much less common in oropharyngeal squamous cell carcinoma than it is in cervical cancer. 5th NGS conference, London, November 19, 2013.

RNAseq to study oropharyngeal squamous cell carcinoma. RNAseq Conference, Lisbon, Portugal, Dec. 6, 2013.

2014
Next generation sequencing and oropharyngeal squamous cell carcinoma. Clinical Genomics Conference, Hansen Wade, Boston, MA, Jan. 29, 2014.

Clinical Genomics Panel Discussion, Chairman, Clinical Genomics Conference, Hansen Wade, Boston, MA, Jan. 30, 2014.

Next generation sequencing and oropharyngeal squamous cell carcinoma. Molecular Pathology Association of India, Mumbai, India, Feb. 14, 2014.

GEN Webinar on Clinical Applications of Next Generation Sequencing, April 17, 2014.

Chairman of CDx Frankfurt, Hansen Wade Meeting on Companion Diagnostics, April 23-24, 2014.

Next generation sequencing and oropharyngeal squamous cell carcinoma. April 25, 2014. University of Heidelberg, DKFZ

Clinical significance of decreased expression of six large common fragile site genes in oropharyngeal squamous cell carcinoma. Presented at the IFNOS meeting in New York, July 29, 2014.

Next Generation Sequencing and how it will transform clinical practice. Road Scholar Presentation at the Mayo Clinic, July 31, 2014.

Using next-generation sequencing to better understand the role that human papillomavirus plays in cancer development. Presented at the International Congress of Genetics-9. Invited lecturer at the BGI meeting in Shenzen, China, September 11, 2014.

Role of human papillomavirus in the development of oropharyngeal squamous cell carcinoma. Presented at the 6th NGS Conference in London, November 20, 2014.

2015
Chairman of RNAseq Europe, Hansen Wade, January 21-22nd, 2015.

History of sequencing technologies, RNAseq Europe, January 21, 2015

Role of human papillomavirus in the development of oropharyngeal squamous cell carcinoma. Presented at the In Vitro Diagnostics Meeting, New Delhi, India, Feb. 6, 2015.

DNA sequencing technologies and using them to understand human papillomaviruses role in cancer. Peter McCallum Cancer Institute, Melbourne, Australia, March 12, 2015.

DNA sequencing revolution and its impact on dentistry. Dental Reviews, Rochester, MN, April 10, 2015.

Next generation sequencing for cancer diagnostics. Presented at the NGS for Cancer Diagnostics Meeting, Philadelphia, PA, May 7, 2015.

Next Generation Sequencing Revolution. Presented at the Next Generation Sequencing meeting, Bali, Indonesia, July 2, 2015.

Next generation sequencing to study oropharyngeal squamous cell carcinoma. Presented at the Clinical NGS Assays, Washington, D.C., August 19, 2015.

Next generation sequencing revolution. Presented at the Sydney Cancer Institute, September 23, 2015.

Next generation sequencing and oropharyngeal squamous cell carcinoma. Presented to the 2nd NGS Conference, Berlin, Germany, October 5, 2015.

Mate-pair sequencing to study oropharyngeal squamous cell carcinoma. Presented at the Big Data Cambridge Meeting, October 21, 2015.

Workshop on Next Generation Sequencing. Presented (and chaired) for the Festival of Genomics, San Francisco, CA, November 4, 2015.

2016
Workshop on Next Generation Sequencing. Presented (and chaired) for the Festival of Genomics, London, UK, Jan. 20, 2016.

Mate-pair sequencing to study HPVs role in cancer development. Molecular Pathology Association of India, Meeting, New Delhi, India, March 12, 2016.

Developing a liquid biopsy to monitor oropharyngeal squamous cell carcinoma patients. Presented at the circulating free DNA meeting, Lisbon, Portugal, April 6, 2016.

Mate-pair sequencing as a powerful clinical tool for cancer patients. Presented at the Biomarker World Congress, Philadelphia, PA, May 18, 2016.

Using mate-pair sequencing to study HPVs role in cancer development. Presented at Genomic qPCR, ddPCR, and NGS Singapore, May 26, 2016.

Workshop on Next Generation Sequencing (presented and Chaired), Festival of Genomics Boston, June 27, 2016.

Using mate-pair sequencing as a powerful clinical tool. Presented at Big Data Boston, September 14, 2016.

The next generation sequencing revolution and its' impact on personalized medicine. Presented at the I.M. Sechonov First Moscow State Medical University, September 26, 2016.

The next generation sequencing revolution. Presented at (and chaired the Session) the Mayo Clinic Center for Individualized Medicine Conference, Rochester, MN, October 5, 2016.

Using mate-pair next generation sequencing to study oropharyngeal squamous cell carcinomas. Presented at the 6th NGS Congress, Singapore, October 11, 2016.

Mate-Pair next generation sequencing as a powerful clinical tool. Presented at the Cambridge Big Data Meeting, Cambridge, UK, October 26, 2016.

How the Mayo Clinic is utilizing next generation sequencing to transform clinical practice. Presented at the World Precision Medicine Congress, Washington D.C. meeting, Nov. 14, 2016.

Mate-Pair Next Generation Sequencing as a powerful clinical tool for patients with oropharyngeal squamous cell carcinoma. Presented at the Precision Medicine Congress, Shanghai, China, Dec. 4, 2016.

2017
Next Generation Sequencing and its impact on clinical practice. Presented at the Festival of Genomics, London, Jan. 31. 2017.

Mate-Pair sequencing to understand HPVs role in the development of OPSCC. Presented at the Molecular Pathology Association of India annual meeting in Bhundaneshwar. Feb. 10, 2017.

Mate-Pair sequencing as a powerful clinical tool. Presented at the LabRoots Virtual Webinar. Feb. 22, 2017.

Mate-Pair sequencing to study the role of HPV in the development of oropharyngeal squamous cell carcinoma. Presented April 26th, BioData West, 2017.

Next generation sequencing at its impact on clinical practice. Presented at the BioData World Congress, London, UK, May 18, 2017.

Mate-pair sequencing to study the role of HPV integration in the development of oropharyngeal squamous cell carcinoma. Keynote presentation, Personalized Medicine Meeting, Beijing, China, June 13, 2017.

Different whole genome sequencing strategies to study HPV and oropharyngeal squamous cell carcinoma. Presentation at the Seoul Genomics Meeting, August 22, 2017.

The DNA sequencing revolution, Presented at the Personalized Medicine Meeting in Moscow, October 11, 2017.

Studying the role that HPV plays in the development of different cancers. Presented at the Personalized Medicine Meeting in Moscow, October 12, 2017.

Different whole genome sequencing approaches to study HPV and its role in the development of oropharygeal squamous cell carcinoma. Presented at the Biomarkers and Clinical Research Meeting, Baltimore, MD, October 19, 2017.

Doing whole genome sequencing on the BGI-500 Sequencing Platform to study HPV and oropharyngeal squamous cell carcinoma. Presented at ICG-12 for BGI in Shenzhen, China. October 26, 2017.

Whole genome sequencing to study HPV and its role in the development of oropharyngeal squamous cell carcinoma. Presented at BioData Cambridge Meeting, November 3, 2017.

HPV and its' role in the development of different cancers. Presented at the World Congress of Virology, Miami, FL, November 21, 2017.

Different whole genome sequencing strategies for the clinical management of patients with oropharyngeal squamous cell carcinoma. Presented at the Molecular Med Tri-Con, San Francisco, CA, Feb. 12, 2018.

Different whole genome sequencing strategies for the clinical management of patients with oropharyngeal squamous cell carcinoma. Presented at the Biomarker Research in Clinical Medicine Conference in Paris, France, Feb. 19, 2018.

Using different whole genome sequencing platforms to characterize cancer genomes and their clinical impact. Presented at the BioData World West Conference, San Francisco, CA, March 13, 2018.

Whole genome sequencing as a powerful clinical tool to treat cancers with an HPV etiology. Preented at the World Precision Medicine Congress, London, UK, May 16, 2018.

The DNA sequencing revolution. Presented at the Road Scholar Mayo Retreat. May 21, 2018.

Whole genome sequencing as a valuable clinical tool for the management of cancer patients. Presented at the Lab Roots Virtual Event, June 5, 2018.

The DNA sequencing revolution and its' impact on clinical oncology. Keynote Lecture at Clinical Oncology 2018, Dublin Ireland, June 11, 2018.

Advances in next generation sequencing and their impact on the study of cancer. Presented at Cancer and Oncotherapy Meeting, Rome, Italy, July 23, 2018.

The DNA sequencing revolution as an important singularity. Presented at the 11th International Conference on Genomics and Pharmacogenomics. Philadelphia, PA, September 21, 2018.

Whole genome sequencing strategies for the management of patients with oropharngeal squamous cell carcinoma. Presented at the 3rd International Papillomavirus Conference, Sydney, Australia, October 4, 2018.

Using whole genome sequencing strategies to study HPVs role in the development of oropharyngeal squamous cell carcinoma. Presented at the International Congress of Genetics-13. Shenzhen, China, October 25, 2018.

The DNA sequencing revolution as an important singularity. Presented at the Precision Medicine Meeting for Aurora Biomed. Guangzhou China, November 15, 2018.

Different whole genome sequencing strategies to study HPVs role in cancer development. Presented at the BioData World Congress 2018. Basel, Switzerland, Nov. 29, 2018.

Next generation DNA sequencing revolution and its' impact on clinical practice. Presented at the Molecular Pathology Association of India 2019 Meeting. Mumbai, India, Jan. 11, 2019.

History of Next Generation Sequencing. Presented at the Festival of Genomics, London, UK, Jan. 24, 2019.

APPENDIX 2: LIST OF DOCUMENTS REVIEWED

In connection with my analysis in this matter I reviewed the following documents:

1. ILMNBGI0024503
2. ILMNBGI0024628
3. ILMNBGI0024755
4. ILMNBGI0024852
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